INDEX NUMBER

Vol. VIII AUGUST, 1933 No. 6

THE AMERICAN HEART JOURNAL

PUBLISHED BI-MONTHLY
UNDER THE EDITORIAL DIRECTION OF
THE AMERICAN HEART ASSOCIATION

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PUBLISHED BY THE C. V. MOSBY COMPANY, 3523-25 PINE BLVD., ST. LOUIS, U. S. A.
Entered at the Post Office at St. Louis, Mo., as Second Class Matter.

The American Heart Journal

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The American Heart Journal

VOL. VIII AUGUST, 1933 No. 6

Original Communications

PRODUCTION OF THE ANGINAL SYNDROME BY INDUCED GENERAL ANOXEMIA*†

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IN INDIVIDUALS subject to attacks of chest pain in whom there are neither physical signs nor electrocardiographic evidence of an appropriate cause, it is often impossible to ascertain the origin of the pain. Chest pain in the individual with a normal heart may be mistakenly diagnosed as angina pectoris. On the other hand the patient with angina pectoris may be assured of a normal heart yet die within a short time of coronary occlusion. The clinical recognition of impaired coronary circulation is therefore difficult as well as important.

Several clinical peculiarities of angina pectoris have drawn our attention and indicate that the pain arises from a localized, sensitive area of myocardium affected by any of a number of stimuli. For example:

1. The pain in some cases appears only at the beginning of effort—the patient is unable to "shift gears" quickly. If the patient makes the same effort but starts gradually he does not develop pain. In explanation, we assume that sudden nutritional demands by the myocardium initiate the pain.

2. Many patients develop pain on exposure to cold. External cold, in this instance, acts as a stimulus.

3. The site of coronary occlusion is localized. The majority of coronary thromboses occur in one area, namely, in that supplied by the anterior descending branch of the left coronary artery.

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†A preliminary report of the results described in this communication was read before the Society for Experimental Biology and Medicine (Rothschild, M. A., and Kissin, M. Proc. Soc. Exper. Biol. & Med. 29: 577, 1932).

‡Aided by a grant from the Herbert L. Celler Foundation.

4. Many patients with angina pectoris are free from pain or have less pain following recovery from an attack of coronary occlusion.[1] This occurs because the localized, sensitive area previously supplied by the occluded artery has been replaced by fibrous tissue (infarction) and is no longer capable of conducting painful sensations.[2]

The theory that angina pectoris is due to stretching of a diseased aorta is losing ground. The opinion prevails today that myocardial ischemia is the cause of the pain.[2] Keefer and Resnik[3] have gone a step further and on theoretical grounds have concluded that myocardial anoxemia is the cause of anginal pain.

These considerations led us to investigate the effect of gradually induced general anoxemia on two groups of individuals, one having impaired coronary circulation, the other having unimpaired coronary circulation. We felt that cardiac anoxemia (which is part of general anoxemia) might be a means of inducing precordial pain and that the response to anoxemia might serve to distinguish between chest pain due to impaired coronary circulation and chest pain arising from other causes.

THE SUBJECTS

Anoxemia was induced in 46 individuals, several of whom were subjected to the experiment twice. The cases were divided into two groups:

A. Control cases.
B. Cases of angina pectoris.

The control group consisted of three sub-groups:

1. Normal individuals with no history of precordial pain, no cardiac symptoms, and no objective signs of cardiac disease. (Normal controls.)

2. Individuals without precordial pain but with subjective complaints related to the circulatory system and with objective evidence of cardiac disease such as valvular defects or hypertension. (Cardiac controls.)

3. Individuals having a history of pain in the left chest not due to impaired coronary circulation; the diagnoses were spondylitis, brachial neuritis, rheumatic carditis, cholecystitis, etc., but not angina pectoris. (Pain controls.)

The cases of angina pectoris consisted of two sub-groups:

1. Individuals with a history of precordial pain and with objective evidence of myocardial disease such as enlarged heart, hypertension, harsh systolic murmurs (due to sclerosis of the heart valves or roughening of the aorta), dilatation or sclerosis of the aorta (determined by roentgenological examination), and electrocardiographic changes suggestive of impaired coronary circulation. (Angina with objective findings.)

2. Individuals with a history of precordial pain but with slight or no objective evidence of myocardial disease. The diagnosis here rested on the evaluation of symptoms. (Angina without objective findings.)

The cases were divided numerically as follows:

Control group 1 (normal)	4	cases
Control group 2 (cardiac)	5	"
Control group 3 (with pain)	11	"
Angina group 1 (with objective findings)	18	"
Angina group 2 (without objective findings)	8	"

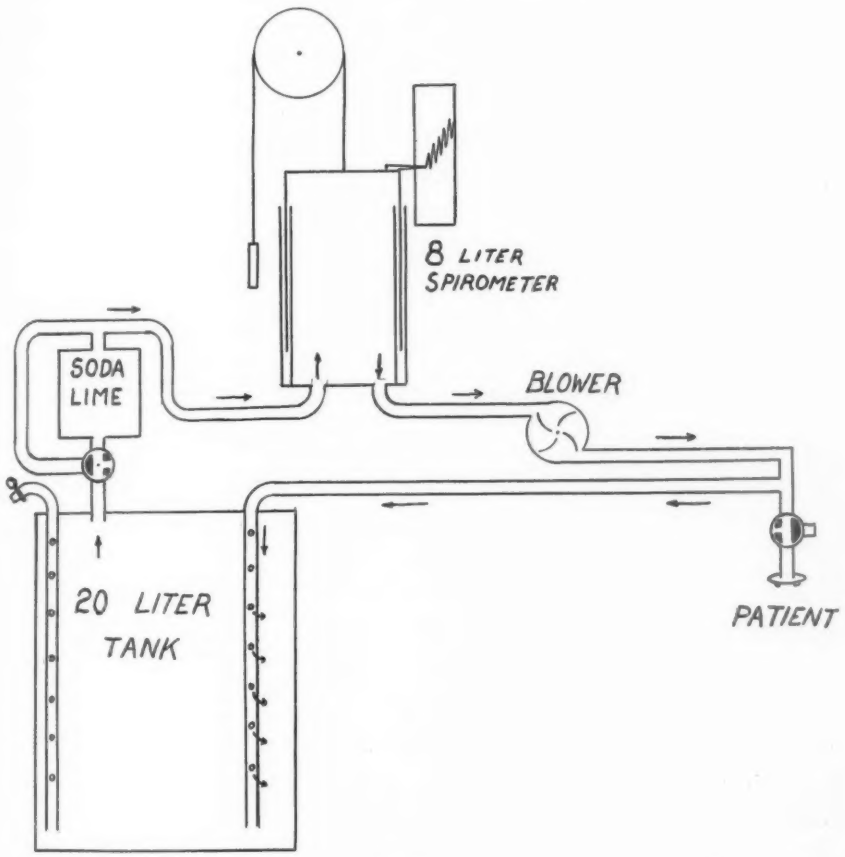

Fig. 1.

METHOD

Anoxemia was induced by rebreathing. The rebreathing apparatus (Fig. 1) was improvised from a basal metabolism spirometer of 8 liters capacity to which was attached in series a 20 liter tank. The rebreathing system contained, therefore, 28 liters in all. A motor blower maintained the circulation. Attached to the top of the larger tank was a

cylinder containing soda lime. At the base of the cylinder was a valve which could be turned to permit the soda lime to be either in or out of the rebreathing system. In this way we could control the absorption of carbon dioxide, either removing it or permitting it to accumulate. A graphic record of the respirations was taken.

Before anoxemia was induced the spirometer was filled with oxygen, and the patient rebreathed an oxygen rich mixture for ten minutes. During this control period the patient was made familiar with the apparatus, was permitted to relax, and was reassured of the harmlessness of the test.

The apparatus was then filled with room or outside air, and electrocardiographic leads were applied to the patient. The confidence of the patient having been won during the control period, he was given an explanation of the procedure to follow. He was told that during the second breathing test he would be uncomfortable, that he might become dizzy, or develop headache, or suffer palpitation, that none of these discomforts would be severe, and that they would disappear as soon as the test was stopped. He was told that these uncomfortable sensations should cause no alarm, that they were an evil necessary for the successful performance of the test. It was explained that certain changes appeared in the electrocardiogram during the breathing test that were not otherwise present and that it was necessary for him to withstand the discomforts so that we might obtain more information about his heart. We further told him that we did not wish him to become too uncomfortable, that when he felt he could no longer tolerate the discomfort he was to raise his hand as a signal to stop. We asked, however, that he continue for as long a time as he could because the longer he breathed through the apparatus, the more information we could obtain.

No mention was made of the chest pain that might develop because we did not wish to influence the patient by suggestion. Furthermore, in order to obtain unbiased results, the operator himself knew nothing of the clinical status of the patient prior to the performance of the experiment.

Questions were asked of the patient after the experiment. Suggestion was carefully avoided as before. He was asked if he had experienced dizziness, headache, or palpitation. Whenever pain had been felt, this was, with few exceptions, volunteered spontaneously. The patient was asked his reasons for not wishing to continue rebreathing. The usual reason was pain or respiratory difficulty. But some of the answers were, to say the least, disturbing.

We were told, for instance, "I was afraid I was going to get an attack of pain," or "My doctor told me that I am not sensitive and I don't know when I feel pain, so I was afraid I was injuring myself

without knowing it," or "You told me it would take ten minutes and I saw that the time was up," or "I saw that the lines on the breathing chart were running together." Such experiments were, of course, discarded.

The disadvantage of the rebreather employed was the inability of the patient to talk during the experiment. Since the breathing tube was in the mouth, the subject had to wait to make comments or complaints until the termination of the test. Ideally, we should like to have had a cabinet or transparent head covering in which the patient might be observed and blood pressures, electrocardiograms, and blood samples taken, yet in which the patient could speak.

For a brief time, we used instead of a rebreathing system, a mask through which a 6 per cent oxygen mixture was administered to the patient. This proved unsatisfactory because anoxemia developed too rapidly. Instead of developing precordial pain, the patient lost consciousness. This sometimes occurred with the rebreathing method of inducing anoxemia. Schneider[4] has shown that when anoxemia is induced rapidly, the symptoms appearing are cerebral, but when anoxemia is induced more slowly the circulatory system responds. Therefore, with our technic we endeavored to establish the period of rebreathing as from 10 to 15 minutes. Actually, the period varied from 8 to 23.5 minutes, except in two cases of 4 and 6 minutes, respectively. The disadvantages of continuing too long were the discomforts of dryness of the throat, pinching of the nose by the nose clamp, pressure of the electrodes or bandages, or lying in one position for too long a time.

At the end of each rebreathing period a specimen of air was taken from the auxiliary tank and examined with the Haldane apparatus for its oxygen and carbon dioxide content.

The oxygen content of the inspired air furnished a good index of the degree of anoxemia. When the oxygen level reached 12 per cent, there were rarely symptoms of oxygen lack. At 11 per cent, anoxemic symptoms occasionally appeared. At 10 per cent, symptoms were almost always present, and at 8 per cent they were always present. Furthermore, by watching the ear for cyanosis, we were able to estimate the degree of anoxemia. At 12 per cent, there was rarely cyanosis; at 11 per cent there was occasionally slight cyanosis; at 10 per cent moderate cyanosis was the rule, and at 8 per cent or less there was marked cyanosis.[5]

Nevertheless, the oxygen level of the blood does not follow exactly the oxygen level of the inspired air. Loewy[6] showed that the oxygen tension in the alveoli sinks to between 30 and 35 mm. of mercury before signs of oxygen lack appear. The percentage of oxygen in the inspired air which gives an alveolar oxygen tension of 30 to 35 mm. varies with the depth of respiration. With shallow respirations, the

inspired air may contain as much as 12 per cent oxygen, while the alveolar tension is 35 mm. With deeper respirations, 9 to 10 per cent oxygen in the air will give an alveolar tension of 35 mm. It is therefore more difficult to render a subject anoxemic if he breathes deeply.

Blood gas studies were not made. In order to study the arterial oxygen, it would have been necessary to puncture an artery. This is frequently painful and adds a psychic factor. Often, too, a minute or more is required before one can obtain the blood sample. Once the patient has signalled for the test to be stopped, a minute is too long a time to continue. Every second is important lest the patient lose consciousness or detach the mouthpiece. Arterial blood determinations were, therefore, not feasible. However, blood gas studies are in order. It remains to devise a technic for collecting blood specimens without interfering with the experiment.

RESULTS

The effect of induced anoxemia in our subjects was as follows:

Control Group	1 (normal),	4 subjects,	0 developed pain
	2 (cardiac),	5 subjects,	0 developed pain
	3 (pain),	11 subjects,	0 developed pain
Angina Group	1 (objective findings),	18 subjects,	11 developed pain
	2 (no objective findings),	8 subjects,	7 developed pain

Of 26 individuals suffering from angina pectoris (impairment of the coronary circulation), 18 developed precordial pain during induced general anoxemia and 8 did not. Twenty control subjects did not experience pain.

Pain appeared when the oxygen level fell to between 11 and 6 per cent. The pain was identical in character and distribution with the pain of which the patient gave a history except that it was generally milder. Occasionally, however, the attack of pain produced was more severe than the spontaneous attacks. A patient who gave a history of pain beginning in the left elbow radiating to the chest, developed a pain in the same site and with the same radiation during anoxemia. Several patients remarked, "This is the same pain that bothers me." The pain subsided, as a rule, as soon as air (20.9 per cent oxygen) was admitted to the lungs. Occasionally, the pain persisted for several minutes after the end of the experiment. On three occasions it was necessary to administer amyl nitrite for relief of the pain.

In order to rule out the possibility that the increased respiratory activity which appears during anoxemia is the cause of the anginal attacks, we investigated the effect of hyperventilation without anoxemia on thirteen individuals who had developed pain during anoxemia. Carbon dioxide inhalations were used to reproduce the deep breathing appearing in the last few minutes of the anoxemic period.

The rebreathing apparatus was filled with oxygen (25 to 40 per cent), and the patient was connected to it. For the first five to seven minutes the carbon dioxide was absorbed, then the valve was turned so that the carbon dioxide accumulated. Almost immediately thereafter an increase in the rate and depth of respiration began and continued progressively until the end of a ten-minute period. The carbon dioxide content of the inspired air at the end of the experiment varied from 1.2 to 3.7 per cent (average 2.1 per cent). Pain appeared in but one case (q.v.) and was caused, without doubt, by the excitement of the experiment.

Several experiments illustrate significant points and are therefore considered individually.

One patient (M. W.) developed an attack of pain during the control period as well as during the anoxemic period of rebreathing. During the anoxemic period he did not become cyanotic (the oxygen level of inspired air at the end of the experiment was 12 per cent); although the attack of pain which developed was much more severe than the attack he experienced during the control period. We attributed both attacks to the excitement of the experiment and did not include him in the series. Clinically, the patient had frequent and severe attacks precipitated by slight excitement.

One patient (Case 34) did not develop pain when he reached an oxygen level of 12.9 per cent. When later the test was repeated and he reached 8.8 per cent, he developed pain. Another patient (Case 36) developed no pain at 7.4 per cent. When the experiment was repeated at a later date, she developed an attack at 9.6 per cent. She gave a history of pain brought on by exertion or excitement on each occasion, but for the month before the second test her condition had been worse. These two cases illustrate that factors in addition to anoxemia, per se, are in part responsible for the production of pain.

One patient (Case 10), a man of forty-three years, with rheumatic heart disease, mitral stenosis, aortic insufficiency, and auricular fibrillation, came into the hospital with acute, severe precordial pain unrelieved by nitroglycerin and ¾ grain of morphine sulphate. The diagnosis of coronary occlusion was made and he was treated accordingly. Several weeks later, the anoxemia experiment resulted negatively for pain, the oxygen level reaching 6.1 per cent. A month later he died, quite suddenly, from cerebral embolus. Post-mortem examination revealed healthy coronary arteries. There was both an old and recent rheumatic infection of the heart.

One patient (Case 38) in whom we were able to precipitate an attack of pain, was classed originally in the group without objective evidence of myocardial damage (angina group 2). Later, electrocardiographic evidence of myocardial damage became overt, the T-wave became flat in Lead I and inverted in Leads II and III, and we changed

the classification to angina group 1, i.e., with evidence of impaired coronary circulation. This indicates the potential value of the anoxemia test in establishing the diagnosis of coronary artery disease while there are only subjective symptoms.

In Case 27, the subject was classed in the series that did not develop pain. However, he did develop a "heaviness of the chest" during anoxemia. The patient gave a history of attacks of "heaviness of the chest" associated with precordial pain. Inasmuch as we were unable to reproduce the attack in its entirety, we omitted this case from the list of those in whom we were able to precipitate an anginal attack.

The experiments were begun two years ago. During the course of developing the technic, more than one hundred tests were made. The patients have been closely followed, and there have been no untoward effects as a result of the experiments.

DISCUSSION

In cases with definite impairment of the coronary circulation we hesitated to continue the experiment beyond the point of evident discomfort. We believe that more individuals would have developed pain had anoxemia been continued. By reference to Table I showing the oxygen levels reached by our cases of angina pectoris, it will be seen that five subjects who did not develop pain did not go below 8 per cent. On the other hand, in the cases that developed pain, it will be noted that pain did not appear at times until the oxygen level reached 7 per cent. In one instance, with a very cooperative and calm patient, pain appeared only at 5.9 per cent. Furthermore, as time went on and our technic improved, the percentage of patients with clinical coronary artery disease in whom we were able to reproduce pain increased. In the first 21 experiments on subjects with angina pectoris, 12 subjects experienced pain, whereas in the last 7 experiments on the same group, 6 subjects experienced pain. In addition, two subjects who did not develop pain at the first trial, at the beginning of our experiments, did later at a second trial.

It is a well-known clinical fact that after cardiac infarction patients frequently have less severe pain than in the prethrombotic stage. This may explain why the definitely anginal group showed such a high per cent that did not develop pain. The stimulus, anoxemia, was inadequate and we were unable to pass the pain threshold.

Further analysis of Table I reveals no relationship between the oxygen level and the onset of pain. We are unable at present to demonstrate an oxygen level at which pain commences or ceases. More important is the relation between the sensitiveness of the patient and the degree of anoxemia necessary to initiate pain. In several instances Libman's pain test[7] was made (unfortunately not in all cases), and it

was found that at least two of the subjects in whom we were unable to produce pain were hyposensitive. A large series of individuals must be studied, however, before final conclusions may be drawn.

TABLE I

OXYGEN LEVEL AT END OF EXPERIMENT IN ANGINOUS CASES

	CASES DEVELOPING PAIN	CASES NOT DEVELOPING PAIN
Group I (with objective evidence of myocardial disease)	6.4%	6.4%
	7.1	*7.4
	8.4	7.9
	8.6	7.9
	8.6	8.0
	†8.8	8.1
	9.4	9.4
	*9.6	9.8
	9.9	†12.9
	11.2	
	11.2	
Group II (without objective evidence of myocardial disease)	5.9	8.7
	8.4	
	8.8	
	8.9	
	9.1	
	9.6	
	9.8	
Average for Groups I and II	8.8	8.5

†, * Same case.

TABLE II

PERCENTAGE OF OXYGEN IN INSPIRED AIR AT END OF EXPERIMENT

CONTROL GROUP I	CONTROL GROUP II	CONTROL GROUP III	ANGINA GROUP I	ANGINA GROUP II
6.1	6 4	6.4	6.4	5.9
7.8	7.8	6.8	6.4	8.4
8.1	8.1	7.0	7.1	8.7
8.9	8.3	7.5	7.4*	8.8
	8.7	7.7	7.9	8.9
		8.1	7.9	9.1
		8.5	8.0	9.6
		8.8	8.1	0.8
		8.8	8.4	
		9.6	8.6	
		10.3	8 6	
			8.8†	
			9.4	
			9.4	
			9.6*	
			9.8	
			9.9	
			11.2	
			11.2	
			12.9†	
Average 7.7	Average 7.9	Average 8.1	Average 8.85	Average 8.6
Average for all control cases 8.0			Average for all anginous cases 8.8	

*, † Same case.

Examination of Table II showing the percentage of oxygen in the inspired air at the end of each experiment, demonstrates no appreciable difference between the oxygen level reached by the controls and by those with impaired coronary circulation. This supports the view that the response to anoxemia is not a test of cardiac function.[8]

One may ask why our control subjects did not experience pain. If myocardial anoxemia is a cause of anginal pain, then any myocardium, damaged or sound, when anoxemic, should be painful. There are several answers to this question. First, the degree of anoxemia in our control subjects, although the same as in our cases of angina pectoris (Table II), may have been insufficient to produce pain. It may be that the heart with a good blood supply requires a greater degree of oxygen deprivation for the initiation of pain than the heart with impaired circulation. Second, it is possible that the hearts of our control subjects were hyposensitive, that there existed no areas of increased sensitivity as in individuals suffering from angina pectoris.* Hence, our stimulus, cardiac anoxemia, could not excite pain. Third, there occurred in our control subjects, during general anoxemia, a compensatory dilatation of the coronary arteries (Hilton and Eicholtz,[9] Gremels and Starling,[10] Hammouda and Kinosita,[11] whereby an adequate oxygen supply to the myocardium was maintained. On the other hand, in our subjects who suffered from angina pectoris, the coronary arteries were sclerotic and rigid and unable to dilate during anoxemia. Hence the myocardium became anoxemic and the patient felt pain.

Table III illustrates that during the control period of hyperventilation without anoxemia, the minute volume of the respiration tended to increase during the last five minutes, and that during the anoxemic period the same increase usually but not always appeared. In other words, the minute volume of the respiration was increased, as a rule, under both conditions. We feel, therefore, that respiratory effort played little or no rôle in the causation of pain.

In addition to lack of oxygen, other factors may affect the heart during anoxemia. During anoxemia, tachycardia develops, the diastolic blood pressure falls,[12, 13] the pulse pressure rises,[12, 13] and the minute volume output of the heart increases.[14-19] One may therefore protest that unless these factors are controlled, it is not possible to hold anoxemia, per se, responsible for the pain. One may insist that the decreased efficiency of the heart during tachycardia, the inability of the heart to make the best use of its nutritive supply, is the cause of the pain. Or one may attribute the pain to the diminished coronary blood flow that accompanies a fall in diastolic blood pressure.[20] The rise in pulse pressure may be held accountable, since a heart works harder

*This lack of cardiac sensitivity may explain why those of our control subjects who had essential hypertension and probably some degree of coronary sclerosis had no pain clinically or experimentally.

TABLE III

VOLUME OF THE RESPIRATION IN LITERS PER MINUTE DURING REBREATHING

CASE	PERIOD	MINUTE																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
30	C*	10.5	11.1	10.5	11.4	10.5	10.6	10.9	10.2	11.2	12.5														
	A*	11.1	11.3	10.9	11.5	11.8	10.7	11.5	11.5	12.0	12.5	15.6	16.6	16.9											
33	C	6.5	6.9	7.1	7.5	8.3	8.2	9.1	9.0	9.5	9.2	10.3	10.2	11.1	10.7	11.1	11.2								
	A	7.3	8.9	9.5	9.1	9.9	10.3	11.0	12.0	12.2															
34	C	9.7	8.3	9.4	9.0	8.7	10.0	9.3	10.1	10.9	12.6														
	A	10.1	10.7	10.0	11.5	11.3	11.9	12.9	14.7	14.8															
36	C	5.0	4.8	5.0	5.1	5.6	5.8	6.0	5.8	6.2	7.7														
	A	4.5	5.5	5.2	5.7	6.8	6.2	6.6	6.5	7.2	6.3														
39	C	9.5	9.5	9.3	9.3	9.2	9.0	9.6	10.6	11.2	12.7														
	A	10.2	10.3	10.4	10.0	10.0	10.6	10.5	9.8	10.4	10.2	9.8	9.6	10.0	10.4	10.9	9.8	10.2	9.7						
40	C	10.8	10.8	10.6	9.9	9.4	8.1	9.5	9.4	9.3	8.4														
	A	8.7	10.0	10.2	8.9	8.6	8.0	7.5	8.2	8.1	8.1	8.5	8.9	8.8	9.2	9.4	9.6	9.9	10.4	10.8	12.3	12.5	17.4	18.6	
41	C	6.0	6.4	7.4	8.2	8.8	8.7	8.6	8.1	9.5	9.8														
	A	8.1	9.6	7.9	6.7	6.9	7.1	7.3	7.4	7.7	7.6	8.2	7.8	7.8	8.0	9.2	9.5	9.4	10.0	10.0					
42	C	7.4	10.3	8.4	9.2	10.6	9.9	8.5	9.8	7.0	7.0														
	A	8.0	7.5	7.5	7.6	8.0	6.8	8.1	7.2	7.4	7.2	7.5	8.2	7.8	9.0	8.3	9.8	10.0							
43	C	7.0	7.5	6.7	7.7	8.8	9.3	8.1	8.0	8.8	8.2														
	A	7.0	7.4	8.1	8.2	10.1	8.9	10.8	10.1	10.4	10.9	9.7	9.4												
44	C	9.5	7.2	7.6	9.6	7.2	8.0	8.5	7.3	7.6	8.7														
	A	7.6	7.4	6.2	5.6	4.9	5.6	4.9	5.6	4.3	6.8	6.2	6.0	5.7	6.0	6.1	5.9	7.0	4.8	6.6	7.4	5.0	6.7	6.0	6.7
45	C	9.0	9.0	10.0	10.0	9.8	9.5	9.6	10.8	11.8	11.8														
	A	9.4	9.7	9.2	9.3	9.3	9.4	10.0	10.0	10.4	11.0	11.8	12.1	13.1											
47	C	17.3	11.7	14.3	11.3	10.5	10.3	10.7	11.3																
	A	10.5	13.3	12.8	16.6	12.4	12.0	10.1	11.0	10.6	9.6	8.2	7.9	6.6	6.2	6.7	8.2								

* C, means control; A, means anoxemia.

when the pulse pressure rises. Finally, the increased work of the heart from a rise in the minute volume output during anoxemia may be held responsible for the pain.

But leaving these considerations aside, we have confirmatory evidence that anoxemia is the cause of the pain, from a recent study[21] by one of us on the effect of anoxemia on exercising skeletal muscle. It was found that oxygen lack is an important contributing cause of the pain experienced in an exercised muscle.

SUMMARY

1. Anoxemia was induced by rebreathing in 26 subjects with angina pectoris (impaired coronary circulation). Eighteen of the 26 experienced an attack of precordial pain. Twenty control subjects did not develop pain.

2. The induced attacks were identical in character with the spontaneous attacks.

3. Anoxemia is in part responsible for the pain of angina pectoris.

4. The response to induced anoxemia is of value in the diagnosis of impaired coronary circulation. Only persons with angina pectoris experienced pain during anoxemia.

After our preliminary note had been issued and after this manuscript had been composed, a report appeared by Dietrich and Schwiegk (Dietrich, S., and Schwiegk, H.: Das Schmerzproblem der Angina Pectoris, Klin. Wchnschr. 12: 135, 1933) confirming our results.

The following are representative protocols:

Case 8, control group II, male, forty-two years old. Three months before the patient began to notice swelling of the ankles which subsided almost completely with rest in bed. Otherwise, he felt well. Physical examination, including the heart and eye grounds, was negative. Urinalysis revealed casts, albumin, and red blood cells; specific gravity 1.010 to 1.022. Basal metabolism: –28, –20, –8, –25. Blood pressure: 110/60. Roentgenogram of the chest showed moderate generalized enlargement of the cardiac shadow and moderate dilatation of the aorta. Electrocardiogram: negative. Diagnosis: *Nephrotic stage of chronic glomerular nephritis.* Anoxemia: The experiment lasted 13.5 minutes. The oxygen content reached 8.3 per cent, the carbon dioxide 0.2 per cent. The heart rate increased from 80 to 130. The experiment was stopped because of difficulty in breathing. There was no precordial pain. The electrocardiogram showed flattening of the T-waves in Leads I and II. The T-wave of Lead III became less inverted. The S-T segment of all three leads showed a drop of about 1 mm. in the last minute.

Case 17, control group III, male, thirty-six years. The patient complained of pains across the chest and down both arms coming in attacks for the past two years. The first attack came while the patient had been playing polo after he had been hit on the left side of his chest with a polo ball. The pain then radiated across the chest and down both arms. There was shortness of breath associated with it. The attack lasted about three hours. He had six attacks since then, the last one a week before while sitting at the desk. The patient felt "as if somebody were tearing

out his lungs.'' There was no sense of pressure. Prostration did not follow the attacks. He was able to go about and do anything during the pain. The patient climbed two flights of stairs six to seven times a day without discomfort. He complained also of a pain in the neck, more on the right side, radiating to the shoulder blade, not related to change in the weather and not relieved by nitroglycerin. Physical examination revealed diseased tonsils from which pus could be expressed. The heart sounds were normal. The right trapezius muscle was tender and spastic. There was tenderness along the right side of the cervical vertebrae. The lungs showed no abnormalities. Blood pressure: 110/90. Fluoroscopy showed the heart to be normal. Electrocardiogram: low voltage. Diagnosis: *Spondylitis of traumatic origin.* Anoxemia: The experiment lasted fourteen minutes, the oxygen level reached 7.0 per cent, the carbon dioxide 0.06 per cent. The heart rate increased from 88 to 105. The experiment was stopped because of difficulty in breathing. Precordial pain did not develop. In the electrocardiogram, there developed flattening of the T-wave in Leads II and III.

Case 18, control group III, male, forty-two years old. At the age of eighteen years the patient suffered an attack of rheumatic fever which required bed rest for three months. The patient had at that time pain in the joints but no fever, nor redness or swelling of the joints. Since that time he had pain in the back. For the past five to six years there had been a steady pain behind the sternum. The pain was no worse on effort. The pain was not present on arising, but as the day went on the pain appeared and became progressively worse. Upon the patient's going to bed, the pain disappeared. There was no shortness of breath on walking. The pain radiated around the left side to the back. Physical examination: The heart was regular and slow, the sounds were of good quality and there were no murmurs. There were no positive findings. Blood pressure: 140/80, 170/110. Roentgenograms showed normal heart and lungs. The esophagus was markedly dilated, and there was spasm of the cordia. Electrocardiogram: negative on two occasions. Diagnosis: *Cardiospasm* (improved with atropinization). Anoxemia: Duration of the experiment twelve minutes, oxygen level reached, 10.3 per cent, carbon dioxide 0.7 per cent. No electrocardiograms were taken. The experiment was halted because of faintness, weakness, and difficulty in breathing. Precordial pain did not develop.

Case 22, Coronary group I, male, fifty-six years old. One and one-half years before the patient had suffered a ''heart attack.'' Since that time he became easily fatigued and short of breath and was compelled to use two pillows for sleep. He had attacks of dull pain in the left side of the chest radiating to the left arm, brought on by exertion. The apex of the heart was in the fifth interspace, 9 cm. to the left of the midline. There was gallop rhythm, and a systolic and diastolic apical murmur. The chest was emphysematous. The liver edge was two fingers below the costal margin. Blood pressure: 140/105. Electrocardiogram: Inverted T-wave in Lead I. Intraventricular block. Diagnosis: *Coronary artery disease.* Anoxemia: The experiment lasted ten minutes. The oxygen reached 9.8 per cent, the carbon dioxide 0.1 per cent. The pulse rate fell from 80 to 70. In the last two minutes, the electrocardiogram showed a drop of 1 mm. in the S-T segment of Lead III. The experiment was stopped because of difficulty in breathing. Palpitation developed, but no precordial pain.

Case 23, Coronary group I, male, fifty-six years old. The patient was diabetic for two years. For six months he suffered mild pain over the heart, squeezing in nature, radiating to the right arm. Eight weeks ago, he suffered a coronary occlusion. He was taken to Beth Israel Hospital where he remained for six weeks. Since discharge from the hospital he felt weak and complained of shortness of breath and mild attacks of pain in the left chest. The pain was less intense than before en-

trance into the hospital. The heart sounds were poor. There were no murmurs. The chest was emphysematous. Blood pressure: 110/78. Electrocardiogram: Low voltage QRS and T in all leads. Diagnosis: *Coronary sclerosis; occlusion with healed infarction.* Anoxemia: The experiment lasted almost twelve minutes. The oxygen level reached 8.1 per cent, the carbon dioxide 0.3 per cent. The heart rate increased from 88 to 97. The test was stopped because of respiratory distress. There was dizziness and headache but no precordial pain. There were no electrocardiographic changes.

Case 31, Coronary group I, male, fifty-one years old. Three months before the patient was in Beth Israel Hospital with an attack of coronary occlusion. He had never had symptoms of heart disease prior to the attack. Since the closure he suffered from shortness of breath and sharp attacks of pain starting in the left elbow and radiating up the arm to the shoulder and then down the left side of the chest. The pain was brought on by excitement or exertion. The pain was relieved by nitroglycerin. The apex of the heart was in the fifth interspace, 10 cm. to the left of the midline. There was a rough systolic murmur heard best over the aortic area. Blood pressure: 106/76. Electrocardiogram: negative. Diagnosis: *Healed infarction of the heart.* Anoxemia: The experiment lasted ten minutes. The oxygen reached 8.6 per cent, the carbon dioxide 0.1 per cent. The heart rate increased from 81 to 103. The test was halted when the patient developed an attack of pain in the left elbow which radiated to the shoulder and down the left side of the chest. This attack was identical with the patient's usual attacks. It was relieved within a minute after air was admitted. In the last three minutes the electrocardiogram showed a drop of 1 mm. in the S-T segment of Lead I and an elevation of 1 mm. in the S-T segment of Lead III.

Case 32, Coronary group I, male, sixty-five years old. For six years the patient had suffered from fatigue, shortness of breath, belching, and pain at the upper end of the sternum. The pain was pressing in nature and radiated to the left arm. It was brought on by exertion and heavy meals and was relieved by nitroglycerin. The apical impulse was not palpable. The heart sounds were of good quality. There was a systolic murmur heard best over the aortic area and another heard best at the apex. Blood pressure: 160/80. Electrocardiogram: Repeatedly negative until one month ago when the T-wave of Lead I became inverted. Diagnosis: *Coronary artery disease.* Anoxemia: Duration eight and one-half minutes. Oxygen level reached 11.2 per cent, carbon dioxide 0.2 per cent. The heart rate increased from 83 to 100. The electrocardiogram showed flattening of the T-wave in Lead I in the last few minutes. The experiment was stopped when the patient developed shortness of breath. He developed a mild attack of precordial pain in the last minute. The pain disappeared as soon as air was admitted.

Case 38, Coronary group I, male, forty years old. The patient, a physician, gave a history of attacks of anginal pain commencing ten months previous to the first examination. The attacks started with a feeling of oppression under the sternum. The pain then radiated to the left shoulder and occasionally to the neck and always down the left arm. The last attack was a week ago after climbing one flight of stairs. The attack lasted about a minute. Nitroglycerin afforded relief. Attacks followed slight exertion. The heart was rapidly pulsating. It was regular. The heart sounds were of good quality and there were no murmurs. Blood pressure: 138/92. Fluoroscopy: Heart and aorta normal. Electrocardiogram: Negative on the first examination when the anoxemia test was performed. Six months later, the tracing showed a flat T-wave in Lead I and an inverted T-wave in Leads II and III. Diagnosis: *Coronary artery disease.* Anoxemia: The experiment lasted eleven and one-half minutes, the oxygen reached 9.4 per cent, the carbon dioxide 0.5

per cent. The heart rate increased from 97 to 108. The electrocardiogram showed a decrease in the height of the T-wave in Leads II and III. During the last minute, the patient developed an attack of pain, identical with his usual attacks, which caused him to terminate the experiment. The pain was not relieved when air was admitted and after one and one-half minutes, amyl nitrite was administered, which gave prompt relief. During the control period the patient was slightly short of breath at intervals but otherwise perfectly comfortable.

Case 41, Coronary group II, male, forty-four years old. Seven weeks before the patient developed a squeezing pain across the chest accompanied by a choking sensation and shortness of breath. The first attack came on while the patient was walking and attacks recurred daily for five days. He was compelled, with each attack, to stop walking. After ten minutes he would be able to go on. The patient could walk slowly as far as he liked but he was unable to walk quickly or up stairs because of the attacks. The heart sounds were of good quality. There were no murmurs. Blood pressure: 150/85. Fuoroscopy: The heart was not enlarged. There was slight rounding of the left ventricle. The aorta was not dilated and the lungs were clear. Electrocardiogram: negative on several occasions. Diagnosis: *Probably coronary sclerosis.* Anoxemia: Duration eighteen and one-half minutes, oxygen level reached 8.8 per cent, carbon dioxide 0.05 per cent. The heart rate increased from 90 to 110. The T-wave of Lead I became flattened. The test was halted when the patient developed an attack of pain in the chest. The pain came on in the last half minute. It was identical with his usual attacks. The pain stopped within a few seconds after air was admitted. During the control period, the patient was completely comfortable.

Case 42, Coronary group II, male, fifty-two years old. The patient complained of pain across the nipples for two months. One year ago he had the same sort of pain. The pain would come on when the patient walked or climbed stairs. There was tingling of the left arm with the chest pain. When the patient stopped walking, the pain disappeared. The heart sounds were slightly distant but otherwise normal. There were no murmurs. Blood pressure: 130/70. Fluoroscopy: Rounding with slight hypertrophy of the left ventricle. The aorta was elongated but not widened. The lungs were clear. Electrocardiogram: Negative. Diagnosis: *Probably coronary sclerosis.* Anoxemia: Duration seventeen minutes. Oxygen 9.8 per cent, carbon dioxide 0.7 per cent. The heart rate increased from 70 to 88. There were no electrocardiographic changes. In the last minute the patient developed precordial pain accompanied by tingling in the left wrist. This disappeared within a few seconds after air was admitted. During the control period, the subject was perfectly comfortable.

Case 43, Coronary group II, female, thirty-nine years old. Four months before the first examination, the patient was laid up with a mild attack of grip. Ten days later, on walking, she felt a pain across the chest. Since that time, there were many attacks. The pain came on after walking about half a block. The pain was burning. It radiated across the chest and down both arms into the elbows. When severe, it radiated to the fingers of both hands. The pain was worse in cold weather. It was especially bad walking against the wind. Climbing stairs precipitated attacks. The pain was accompanied by shortness of breath. At the age of seventeen years the patient was told that she had inflammatory rheumatism. The heart was regular and rapid. There was a systolic murmur at the apex, louder on exercise. Blood pressure: 140/90. Fluoroscopy: The heart was not enlarged. There was no evidence of mitral disease. Electrocardiogram: Negative. Diagnosis: *Impaired coronary circulation.* Anoxemia: The test lasted sixteen minutes, the oxygen reached 9.6 per cent, the carbon dioxide 0.02 per cent. No electrocardiograms were taken.

In the last minute the patient developed pressure on the chest, "like the pains I get when I walk." The pain increased in severity so that the subject signalled to halt the test. The pain lessened as soon as air was admitted, but it did not disappear for three minutes. During the control period the patient was perfectly comfortable.

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INDUCED GENERAL ANOXEMIA CAUSING S-T DEVIATION IN THE ELECTROCARDIOGRAM*†

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IT WAS reported in a previous communication[1] that the subjective response to anoxemia of individuals with angina pectoris differed from the response of control subjects. Subjects with angina pectoris developed precordial pain during exposure to atmospheres of low oxygen tension; control subjects did not. We felt that there might appear during anoxemia an objective finding which would aid in distinguishing between the two groups. We therefore investigated the electrocardiographic changes during anoxemia in subjects with and without angina pectoris.

METHOD

Anoxemia was induced by rebreathing, with the technic described in a previous publication.[1] Thirty-eight individuals were studied. The subjects were divided into two groups. The control group consisted of 14 individuals without clinical evidence of impaired coronary circulation; the other group consisted of 24 individuals with angina pectoris.

A three-lead electrocardiogram was taken before the subject had begun to rebreathe. Two minutes after the start of rebreathing, records of the three leads were taken in rapid succession. As a rule, one could take a strip about 7 inches long (seven seconds) of each lead and finish within thirty-five or forty seconds. Tracings were taken every two minutes for the first ten minutes, then every minute until the close of the experiment. If the patient became cyanotic or showed signs of anoxemic distress during the first ten minutes, tracings were taken every minute after that time instead of waiting for ten minutes to elapse. One minute after the period of anoxemia another set of tracings was taken, and again, in most instances, three minutes after the anoxemic period had come to a close.

At the end of the experiment a sample of air was taken from the rebreathing chamber and its oxygen content determined with the Haldane apparatus.

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†A preliminary report of the results described in this communication was read before the Society for Experimental Biology and Medicine (Rothschild, M.A., and Kissin, M.: Proc. Soc. Exper. Biol. & Med. 29: 577, 1932).

‡Aided by a grant from the Herbert L. Celler Foundation.

If the resistance of the patient was high, overshooting of the galvanometer might occur, and produce after a high R-wave, a downward deviation of the R-T (S-T)* segment which is only artefact. In order to obviate such distortion, we took care that the resistance of the patient was 2,000 ohms or less by cleansing the skin with alcohol,

TABLE I

SUMMARY OF RESULTS OF ANOXEMIA

CASE NUMBER	GROUP	OXYGEN IN INSPIRED AIR	PAIN	S-T DEVIATION
1	Control I	8.1%		+
2	" I	8.9		No Ecg.
3	" I	7.8		No Ecg.
4	" I	6.1		
5	" II	6.4		+
6	" II	8.7		
7	" II	7.8		No Ecg.
8	" II	8.3		+
9	" II	8.1		
10	" III	6.8		No Ecg.
11	" III	8.8		
12	" III	6.4		No Ecg.
13	" III	8.1		
14	" III	7.5		
15	" III	8.5		
16	" III	8.8		
17	" III	7.0		
18	" III	10.3		No Ecg.
19	" III	9.6		
20	" III	7.7		
21	Angina I	8.0		
22	" I	9.8		+
23	" I	8.1		
24	" I	9.4		
25	" I	7.9		
26	" I	6.4		+
27	" I	7.9		
28	" I	6.4	+	
29	" I	8.6	+	
30	" I	8.4	+	
31	" I	8.6	+	+
32	" I	11.2	+	
33	" I	11.2	+	+
34	" I	12.9		
34	" I	8.8	+	+
35	" I	9.9	+	
36	" I	7.4		+
36	" I	9.6	+	
37	" I	7.1	+	
38	" I	9.4	+	
39	" I	8.7		No Ecg.
40	" II	5.9	+	+
41	" II	8.8	+	
42	" II	9.8	+	
43	" II	9.6	+	No Ecg.
44	" II	8.4	+	
45	" II	8.9	+	+
46	" II	9.1	+	

*S-T will be used throughout for convenience.

rubbing the skin, using hot bandages, and preventing the salt solution from drying by wrapping rubber pads around the bandages.

RESULTS

Three of 14 control subjects developed changes in the S-T segment. Of these three, two were patients without precordial pain but with evi-

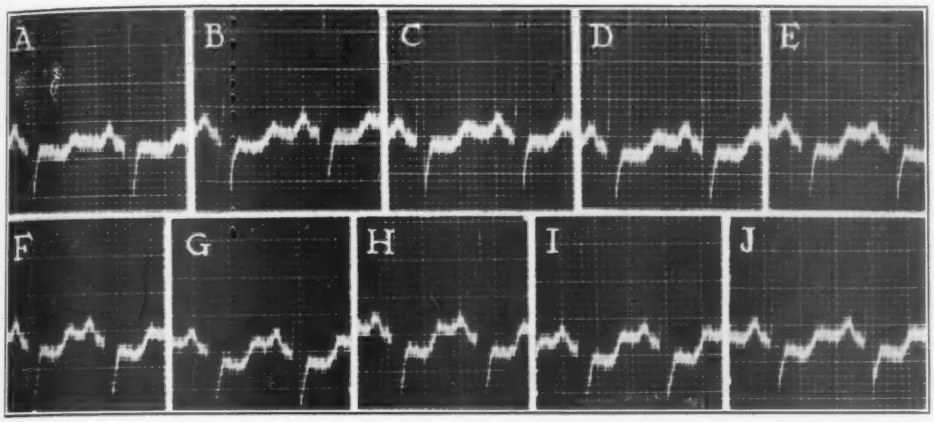

Fig. 1.—Lead II of Case 33.

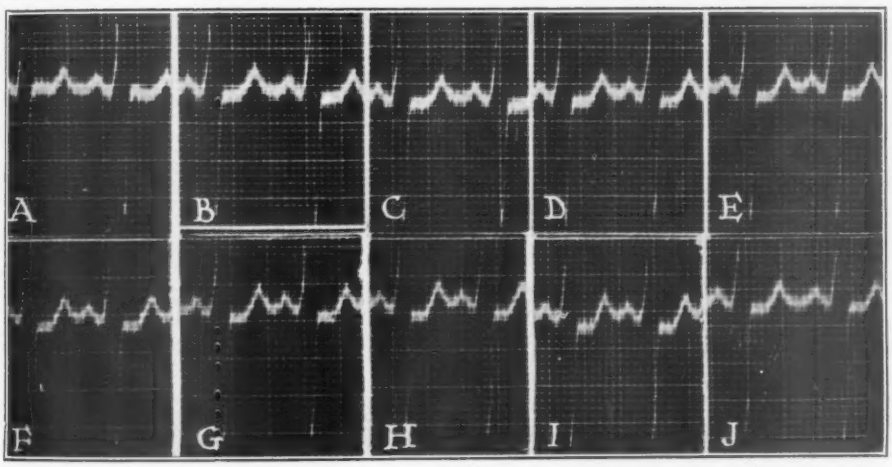

Fig. 2.—Lead III of Case 33. *A*, Before anoxemia; *B*, after one minute of rebreathing; *C*, two minutes; *D*, three minutes; *E*, four minutes; *F*, five minutes; *G*, six minutes; *H*, seven minutes; *I*, eight minutes; *J*, one minute after the end of the anoxemic period. Note the depression of the S-T interval after the first minute of rebreathing.

dence of myocardial disease, and one was a man of twenty-six years without signs of heart disease. Eight of 24 subjects with angina pectoris developed a deviation of the S-T segment.

The relationship between precordial pain[1] and the S-T change is shown in Table I. Of the 24 anginal subjects whose electrocardio-

grams were taken during induced anoxemia, eight developed distortion of the S-T interval. Five of these eight developed pain as well. In 12 anginal subjects pain appeared but no S-T change.

The change in the S-T segment appeared toward the end of the rebreathing period, as a rule, and became more marked as the degree of anoxemia increased. As soon as the anoxemic period was ended, the phenomenon began to disappear. We did not follow the full course of its disappearance, but in most instances the S-T interval reached its original level within three minutes, often within one minute.

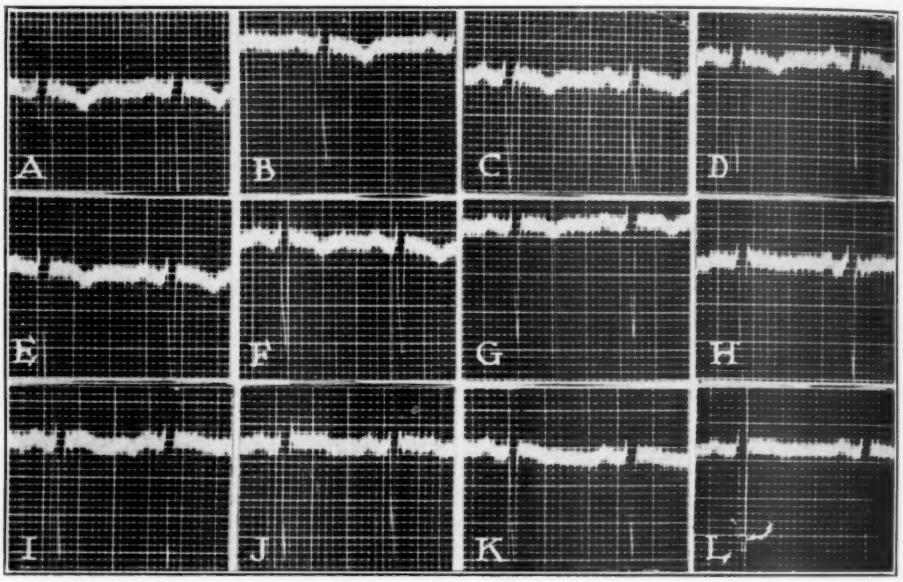

Fig. 3.—Lead III of Case 31. *A*, Before anoxemia; *B*, after one minute of rebreathing; *C*, two minutes; *D*, three minutes; *E*, four minutes; *F*, five minutes; *G*, six minutes; *H*, seven minutes; *I*, eight minutes; *J*, nine minutes; *K*, ten minutes; *L*, one minute after the end of the anoxemic period. Note the elevation of the S-T segment in the eighth, ninth, and tenth minutes.

The S-T deviation was always downward, except in one case which showed an upward deviation in Lead III (Fig. 3). The deviation of the S-T interval from the isoelectric line varied from 0.5 to 2.5 mm. In two cases the distortion appeared only in Lead II, in one case only in Lead III, in four cases in Leads I and II, in two cases in Leads II and III, and in one case in all three leads. In one case there was a downward deviation in Lead I and an upward deviation in Lead III. Figs. 1 to 5 illustrate representative tracings.

The oxygen content of the inspired air varied in those showing S-T changes from 5.9 to 8.9 per cent, with two exceptions. Cases 22 and 33 did not fall below 9.8 and 11.2 per cent respectively. The last two

figures were in cases of intraventricular block. Oxygen levels reached by those exhibiting no distortion of the S-T interval varied from 6.1 to 12.9 per cent (Table II).

One patient (Case 34) developed S-T deviation when he reached an oxygen level of 8.8 per cent, but when on a previous occasion the final level was 12.9 per cent, no change appeared. Similarly, in Case 36, no change in the S-T segment appeared in one experiment when the oxygen level fell only to 9.6 per cent, but in another experiment deviation appeared with a final level of 7.4 per cent.

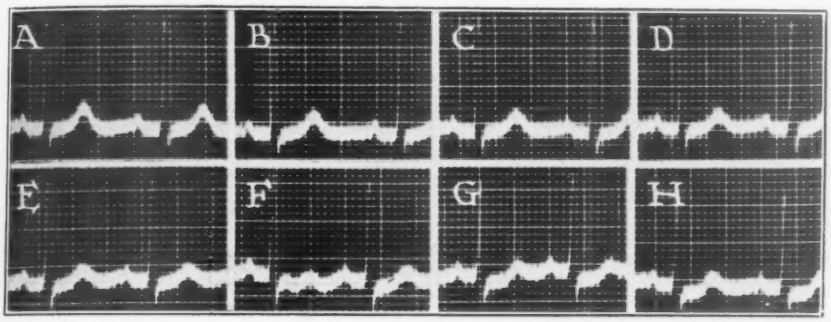

Fig. 4.—Lead I of Case 40.

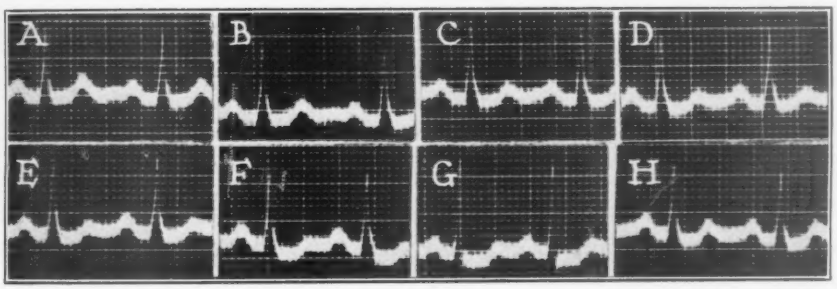

Fig. 5.—Lead II of Case 40. *A*, Before anoxemia; *B*, after ten minutes of rebreathing; *C*, fifteen minutes; *D*, seventeen minutes; *E*, eighteen minutes; *F*, twenty minutes; *G*, twenty-one minutes; *H*, one minute after the end of the anoxemic period. Note the depression of the S-T segment in the seventeenth minute and thereafter.

We endeavored in one instance to reproduce the S-T change that appeared during anoxemia in a case with intraventricular block. First, we tried the effect of inhaling mixtures rich in oxygen and carbon dioxide. Second, we administered atropine intravenously to produce a tachycardia. Third, we gave epinephrin subcutaneously for its reputed ability to increase the work of the heart. Fourth, we administered pitressin for its vasoconstrictor effect. Fifth, amyl nitrite was tried for its vasodilator action. Oxygen and carbon dioxide caused no side actions; atropine caused tachycardia, dryness of the mouth, and mydroasis; epinephrin caused palpitation and a tremor of the hands; pitressin produced a greenish pallor and called forth a desire

TABLE II

FINAL OXYGEN CONTENT OF INSPIRED AIR IN SUBJECTS THAT DID AND DID NOT DEVELOP S-T DEVIATION

CONTROL GROUP		ANGINA GROUP	
S-T CHANGE	NO CHANGE	S-T CHANGE	NO CHANGE
6.4%	6.1%	5.9%	6.4%
8.1	7.5	6.4	7.1
8.3	7.7	*7.4	7.9
	8.1	8.6	7.9
	8.1	†8.8	8.0
	8.5	8.9	8.1
	8.7	9.8	8.4
	8.8	11.2	8.4
	9.6		8.6
			8.8
			9.1
			9.4
			9.4
			*9.6
			9.8
			9.9
			11.2
			†12.9
Average 7.9	8.1	8.4	8.9

Average for all showing S-T changes - - - - - - 8.2%
Average for all not showing changes - - - - - - 8.7

*, † Indicates same case.

to defecate; amyl nitrite produced flushing of the skin and headache; but none caused a deviation of the S-T segment.

DISCUSSION

It is clear that the electrocardiographic change in question, namely, S-T deviation, occurs in individuals with normal coronary circulation as well as in individuals with impaired coronary circulation. But the change appeared more frequently, in our series, in those with impaired coronary circulation. It is probable, too, that hearts with impaired circulation are more sensitive to oxygen lack than are normal hearts, that the S-T distortion appears at a higher oxygen tension in the ischemic heart than in the normal. This is indicated in the two cases (22 and 33) of intraventricular block, mentioned above, in which S-T deviation appeared at a comparatively high oxygen level.

Electrocardiographic changes other than S-T deviation appear during anoxemia. These changes, such as flattening of the T-wave and increase in the height of the P-wave, were described by Greene and Gilbert[2, 3] and Ward and Wright.[4] Lewis and Mathison,[5] Mathison,[6] von Ángyán,[7] Lewis, White and Meakins,[8] Haggard,[9] and Colvin[10] reported auriculoventricular heart-block during asphyxia. Mathison,[6] Greene and Gilbert,[1] and Resnik[11] observed the same finding during induced anoxemia. None of these authors made note of S-T distortion. However, Kountz and Gruber[12] described deviation of the S-T inter-

val in dogs during general anoxemia and Kountz and Hammouda[13] reported the same finding in perfused dogs' hearts that had been asphyxiated. Katz and Hamburger[14] have noted this finding in 20 normal persons during anoxemia.

The changes in the S-T segment that appear during anoxemia are identical with those observed during attacks of angina pectoris.[15-21] Similar findings have been noted in persons with rheumatic fever,[22-26] coronary occlusion,[27-35] uremia,[36] and pneumonia.[37-40] Pericardial effusion, clinical and experimental, has resulted in deviation of the S-T interval.[41-45] Similar changes have been described following experimental occlusion of the coronary arteries[46-55] and of the coronary sinus.[56] Feil, Katz, Moore, and Scott[57] found no characteristic change in the S-T interval following the ligation of the descending branch of the left coronary artery in dogs, but when, in addition, they ligated the inferior vena cava typical deviations appeared. Distortion of the S-T segment has been produced by direct injury to the myocardium or by the injection of caustic substances into the myocardium.[58-62] Electrocardiograms taken during experimental anaphylaxis have shown this change.[63] Similar findings have been noted after the administration of epinephrin,[64] insulin,[65-69] digitalis,[70,71] and pitressin.[72, 73]

SUMMARY

Electrocardiograms of 38 individuals were taken during the induction of progressive anoxemia. Eleven subjects developed deviation of the S-T segment. Eight of the 11 suffered from angina pectoris, three did not. The deviation of the S-T segment was usually downward but in one case was upward. The degree of deviation was related to the degree of anoxemia. No qualitative electrocardiographic finding appeared during anoxemia that will serve to distinguish between individuals with unimpaired coronary circulation and those with impaired coronary circulation.

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ANGINA PECTORIS. A PLEA FOR GREATER OPTIMISM IN PROGNOSIS

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THIS is a plea for the more cautious use of the terms "angina pectoris" and "coronary thrombosis" and for a more optimistic attitude toward patients included in these categories. In the mind of the average layman the first of these phrases has for many years carried the implication of complete and incurable invalidism and sudden death, and recently the second has entered common parlance and in the view of the man in the street holds an equally sinister significance.

Physicians make use of the term "angina pectoris" so frequently that it seems as if almost any chest discomfort may be labeled with this diagnostic tag. It is used nearly as nonchalantly as was the term "malaria" before the days of the discovery of the plasmodium and with almost as little thought as is employed today in assigning respiratory infections and abdominal disturbances to that all-embracing term "influenza." In the last decade we doctors have become, as a recent writer[1] has expressed it, "coronary conscious," and apparently we are now swinging from the Scylla of nonrecognition to the Charybdis of easy going, loose thinking in making this diagnosis. This is particularly regrettable since such a statement conveys to the patient the impression that he is suffering from what is generally regarded as a grave heart condition from which recovery is impossible, which is totally incapacitating and in which death may be imminent at any moment. These labels differ from "malaria" and "influenza" in that these latter conditions are commonly regarded rather lightly by the patient and carry a reasonable assurance of a complete cure.

One would think from the literature, from discussions at medical gatherings and from conversations with many members of the profession that the diagnosis of "coronary thrombosis," and the proper selection of individuals who should be grouped as suffering from "angina pectoris" are simple matters. This I believe is a very erroneous idea.

It is not, in my experience, uncommon to see patients who have been told that they have "angina pectoris" or "coronary thrombosis" who present no objective evidence whatever of an organic defect of the heart or aorta. The heart is of normal size and the sounds are of good quality; there are no murmurs. No friction sound has been heard. As far as can be determined by physical examination or x-ray

studies, the aorta is normal. The blood pressure is normal. There is no definite record of an abnormal heart rate, fever or leucocytosis. The electrocardiogram is normal. The whole evidence offered is a statement of his subjective sensations made by the patient. In many instances an acute attack has not even occurred under the observation of a physician. Many members of this group have a history and other evidences of a highly organized nervous system, and they react with abnormal violence to minor physical or mental stimuli. The evaluation of this subjective evidence is sometimes made even more difficult by the fact that some of these individuals have a subconscious desire to secure sympathy and for this reason would gladly be regarded as chronic invalids, others depressed by the condition of their business affairs would not be sorry to secure financial relief from the operation of a disability clause in an insurance policy. Such conditions undoubtedly act as strong incentives which, consciously or unconsciously, tend to color the story which may be the only evidence upon which the diagnosis must rest.

Let me make myself clear. I do not contend that a man who presents such a picture may not be suffering from "angina pectoris" or even from "coronary occlusion," but I do insist that under such circumstances the true evaluation of the condition is at times most difficult, that a snap diagnosis is not justified and that one should reach a decision only after prolonged and careful study and a most thoughtful analysis of the available evidence.

In considering the condition of patients in whom a heart defect is suspected (this applies also to those with a definitely established diagnosis of heart disease), the psychic element is too often neglected. Most persons are deeply disturbed by any suggestion that they have an abnormal heart. As Conner[2] has expressed it, "the reaction to doubt concerning the integrity of the heart seems to be much more violent and profound than is the case with any of the other internal organs." This is particularly in evidence in patients who are nervously unstable, who have a morbid concern for their state of health, who are easily subject to suggestion and are prone to introspection, but is not limited to these groups, for the nonemotional, well balanced type of individual may be intensely shocked by an intimation that there is an imperfection in this organ, of such vital importance to his health and well-being. There are many sources from which these psychic traumata may come; common among these are the various sensations in the region of the heart of which the patient is conscious, such as pain and palpitation, tachycardias and arrhythmias, the sudden death of a close friend or a member of the family which has been attributed to heart disease, the injudicious statement of a life insurance examiner, or most often of all, the unguarded verdict of the physician who has been called in for an emergency.

The caution which one should employ is illustrated by the following case:

Mr. F. was a man of fifty-five years, who in January, 1927, came to see me complaining of paroxysmal attacks of severe precordial pain radiating to the left arm, which had been troubling him for six weeks. The pain came on only upon walking and stopped after resting for a minute. His descriptions of the paroxysm were in detail quite characteristic of attacks of "angina pectoris." Physical examination showed nothing abnormal except that the heart sounds were a little indistinct and the fluoroscopic findings suggested an aorta that was a trifle wide for a man of his build. The blood pressure was normal. The electrocardiogram was normal. The urine showed a heavy trace of albumin and a few red blood cells, which had been found off and on over a period of twenty years. He was of a high strung, nervous type, worried by heavy business responsibilities. He was paralyzed with fear by his physical condition, expecting a fatal termination at any moment and was preparing to retire from business to resign himself to the life of an invalid. Further questions brought to light the story of an intimate friend who had suffered from "angina pectoris" and had died suddenly ten days before our patient had first noticed his substernal pain. Mr. F. had always used alcohol and tobacco in considerable quantities; he had discontinued the use of both soon after his first attack of pain, but he still continued the use of strong coffee, three to five cups a day. Every effort was made to reassure him; he was advised against closing up his business which he could ill afford to do, was told to take a complete rest in Florida for six weeks and was advised to discontinue the use of coffee. Subsequent events proved that the advice which had been given (it must be confessed with considerable mental reservation) was justified. In the course of a few weeks the pain entirely disappeared, and at the present time he is perfectly well, living a normal life and following his usual business activities.

The difficulties of formulating a correct prognosis in an individual patient is generally recognized. To the physician, statistics may be of value in orienting his general ideas in regard to this group of patients as a whole, but he will be led into a quagmire if he attempts to apply the figures thus obtained to the individual case. Even the life insurance companies (for which the statistical method has made sound business possible) have realized the inadequacy of this method when dealing with the individual claiming disability for "angina pectoris" and "coronary thrombosis."

Statistics and dramatic experiences with sudden death occurring soon after an examination which had revealed very little objective evidence of an organic lesion, have developed a pessimism in physicians which directly or indirectly is all too often conveyed to the patient, destroying his morale and inducing an apprehension devastating to his career.

If we are to be of real service to our patients, this situation demands a guarded optimism; pessimism is out of place. We have legitimate grounds for assuming a hopeful attitude in the individual case. Granting that an accurate prognosis for the individual is impossible, we

still are justified in assuming that a given patient is likely to complete years of useful living and may not be the one limited to a brief period of suffering and invalidism. I feel warranted in taking this attitude, since I am seeing from time to time a very considerable number of patients in whom I feel that the history, physical signs, and course of events observed over a long period have warranted me in making a definite diagnosis of "coronary thrombosis" or of grouping them under the syndrome of "angina pectoris," and who are living ten or fifteen years after the first attack. An occasional patient has been entirely relieved of symptoms of every kind; some are doing full work with only occasional discomfort; others are living a life of limited activity with a modest amount of work and many interlarded hours of pleasure. Fifteen years of even a very restricted life for a man fifty-five or sixty years of age is not so bad, and this may be the lot of any one of these cases.

A case of interest in this connection is that of a man sixty-nine years of age who came under my care because of a severe lobar pneumonia which proved to be fatal. In securing his history he gave me a very vivid description of having had when fifty-one years of age a severe and prolonged attack of substernal pain and other symptoms which strongly suggested the picture of "coronary thrombosis." Following this he had a number of attacks of substernal pain which gradually became less severe and less frequent, until at the end of two years they entirely disappeared. During this period he was able to do a moderate amount of work, and after the complete subsidence of the pain he gradually resumed full activities and was able to carry on a large and important law practice. After the patient succumbed to pneumonia, the autopsy showed a heart that was slightly enlarged, with some calcification of the coronaries and near the lower part of the left ventricle an area of fibrosis and calcification, evidently the residuum of an old infarct, thus verifying the lesion which his history had suggested. The impressive part of this picture is the fact that this heart was able to recover from such an insult sufficiently to support life for sixteen years without symptoms referable to the circulation.

A very similar case of a man who had an attack of "coronary thrombosis" at the age of sixty-three years, and thereafter lived for seventeen years with periods of remarkable physical activity, has recently been reported by White.[3] In their study of "coronary thrombosis," Conner and Holt[4] report one patient as living and well seventeen years after the original attack and several patients who had lived for over ten years. White and Bland[5] have had three patients under observation with anginal attacks for twenty years or more. In his discussion of "coronary occlusion," Krehl[6] says "such a lesion is perfectly compatible with the continuation of life . . . he lives on and may never suspect what an abyss he has escaped."

It is helpful at times, to lay aside one's personal experiences, such as have been presented in this paper, and to review the facts presented

by an acute, independent observer who is unbiased by the impressions which have been gradually forcing themselves on one's own mind. I have recently analyzed the case histories published by Mackenzie[7] in his book *Angina Pectoris*. He records the histories of 147 patients which he classified as "primary angina pectoris." Of these, one man was living thirty-one years after his first attack, still following his trade of a joiner; three had lived twenty-five years or more; one had lived twenty years; seven for fifteen years or more, and twenty-one for ten years or more. This makes a total of 33 individuals who lived for more than a decade after the first paroxysm of pain, and, at the time the report was published, 16 of them were still alive. That the patients of this group of 33 did not die young is indicated by the fact that the average age of those still alive was sixty-four years, and the average age of those dead was seventy-one years. It should be noted also that in a number of these cases death was due, not to angina, but to such conditions as carcinoma, gangrene of a leg, apoplexy, etc. It is further recorded that in the periods following a definite classification as cases of "angina pectoris" a number of these patients were able to play golf without discomfort, one man was "shooting" as had been his custom, there were a trained nurse and a supervisor of nurses both doing regular hospital work, a builder active in his vocation, a man whose travels took him to Florida, Mexico, Argentina and across the Andes at an elevation of 10,000 feet, another who made business trips to Russia, China, Australia and America. There were eight physicians, five in active practice and the others doing a limited amount of work.

This discussion has intentionally avoided an attempt to consider in separate groups cases of coronary thrombosis with anginal symptoms and cases of angina pectoris associated with other pathological or toxic factors. Such a differentiation can often be made promptly; in other instances it may be made after prolonged observation and study, at times it will be made only at the post-mortem examination or perhaps not at all.

From the standpoint of the physician the syndrome of "angina pectoris" should always be taken seriously, but this label should never be attached without due thought and study. Whenever possible this term should be withheld from the patient, for it hangs above him like the sword of Damocles destroying all the possible joys of the banquet of life. As a rule, much less terrifying phrases can be used to secure the necessary cooperation. The prognosis should always be tinctured with hope, for any given individual may be the one to whom is allotted, as in the cases cited above, years of reasonable activity and comfort.

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ARTERIAL HYPERTENSION AND ARTERIOSCLEROSIS ASSOCIATED WITH RAYNAUD'S SYNDROME*

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PATIENTS with arterial hypertension, with or without clinically detectable arteriosclerosis, complain at times of periodic attacks of coldness of the fingers and toes, associated with pallor or cyanosis, with pain or paresthesia, and with temporary weakness of the hands and feet. The attack is usually precipitated by low temperature of the surroundings or by work; emotions play no rôle, in our experience. Spasm of other parts of the vascular tree is not necessarily present. In mild form this syndrome is not infrequent; in severe form it is comparatively rare. Its clinical characteristics resemble strikingly those of classical Raynaud's disease.

So far as we are aware, no information is available as to the physiological mechanism of this syndrome. This communication presents observations on a patient who exhibited severe attacks, in the hope that the study will throw light on the nature of the attack.

REPORT OF CASE

A sixty-eight-year-old, retired railway worker entered the hospital on October 8, 1930, with the complaint of numbness and blanching of the hands. Ten months previously he began to have attacks of numbness and tingling of the two small toes of the left foot, coming at any time, but more often after exertion and in cold weather. At first the attacks would last but a few minutes, but later they increased in number and severity until he was having several daily. He did not know whether there was any change in the color of the skin associated with them. His feet were cold most of the time. Nine months before entry he began to have similar attacks in the hands, which almost always occurred bilaterally. He first experienced numbness of the fingers, which would become pale or blue. After from ten to fifteen minutes the pallor or cyanosis would be replaced by pinkness, and the numbness by tingling. Exposure to cold and undue exertion seemed to be the chief precipitating factors; emotions had no effect. Between attacks his hands were at times slightly blue and cold.

For five months he had noticed that he became fatigued easily, and was subject to increasing dyspnea on exertion. Family and past histories were irrelevant.

Physical examination showed an enlarged heart and supracardiac dullness, with normal sounds except for an accentuated aortic second sound. The arterial blood pressure was 184 mm. Hg systolic and 102 mm. diastolic. There was marked peripheral sclerosis, with tortuosity and beading of the vessels of the extremities, but good pulsation of the dorsalis pedis arteries was noted. It was observed that on

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exposure to cold his hands and feet became cyanotic and cold, while in a warm room they were of normal color and warmth. The results of the remainder of the examination were unessential.

The laboratory tests showed nothing abnormal except for a secondary anemia of 3.5 million red blood cells per cubic millimeter, with 51 per cent hemoglobin.

CLINICAL STUDIES

Induction and Nature of Attacks.—When the hands were placed in water at 22° C., no change was observed. Putting the hands in water at 18° C. for five minutes usually precipitated an attack. A temperature of 15° C. always precipitated an attack, and this temperature was ordinarily employed in the subsequent work in producing attacks. Immersion in water at 12° C. or lower produced either no attack or a very transitory one, to be quickly replaced by a pink flecking associated with increase in skin temperature. A given stimulus (cold) usually produced a more intense and lasting attack in the right hand than in the left, although the minimal stimulus was about the same for the two hands. The patient subjectively had previously noted no difference in the character of the attacks between the two hands.

In these induced attacks the fingers were chiefly involved, the thumbs and the palms only slightly. On removing the hand from the cold water to room temperature (24° to 26° C.) one or more fingers were usually very pale and blanched, while the others were cyanotic. After a few minutes the pallor of the fingers was often replaced by intense cyanosis. The attacks would last from twenty to forty minutes after removal of the hand from the cold water and would clear gradually. The end of the attack was indicated at first by small mottled areas of pinkness which spread and increased in number until the whole finger was pink. Finally, the entire hand would become pink and warmer than normal, as indicated by skin temperature measurements. Occasionally, usually after prolonged immersion in water between 15° and 18° C. or in water considerably below 15° C., one or more fingers or the whole hand would be pink but cold; later they gradually changed to a pale or cyanotic color; such an attack ended with pink and warm skin. The same hand did not always go through quite the same sequence in developing attacks. Producing an attack in one hand by putting it in water never caused one in the other hand through vasomotor cross reflexes, and immersion of the elbow alone or of the arm above the hand in cold water did not cause an attack over the immersed areas or in the hand. None of the above-described experiments produced a change in the brachial and radial pulsations.

When an attack with blanching of a finger had been induced, holding the hand in a dependent position for several minutes or the application of a venous tourniquet for not more than five minutes did not relieve the blanching.

Ulnar anesthesia by infiltration of the nerve at the elbow with novocaine had no influence either on the production or on the nature of the attacks.

Observations on the Capillaries.—The purpose of these observations was to correlate the morphological state of the capillaries of the nail bed and the character of the blood flow with the appearance of the fingers. A special microscope was used for these observations, and each observation was repeated several times.

When a finger was blanched, very few capillaries were visible, and the venous ends of the capillary loops were unusually narrow. There was no flow through the capillaries. When the finger was cyanotic, numerous capillaries were visible, full of blood, but there was either no flow or at most a slow and intermittent flow. When a finger was pink but cold, the capillaries could be observed in great number but the flow was either absent or extremely slow. Often red blood cells stagnating in clumps were visible. When the finger was pink and warm, many capillaries were open and the flow through them was much more rapid than in the normal state.

It is apparent that a bright pink color of the skin may be associated with either of two diametrically opposed states of the blood flow: either very rapid capillary blood flow with normal tissue metabolism, or sudden slowing of the blood flow in the presence of unusually low tissue metabolism. This latter state, occurring in chilled extremities, allows the red blood corpuscles to contain a high content of oxygenated hemoglobin in the venous ends of the capillary loops and in the subpapillary venous plexuses which are responsible for skin color.

The Effect of Vasodilator and Vasoconstrictor Substances.—The following substances were given in doses sufficiently large to produce their full systemic effect, but in no case did they either relieve or alter an attack already present or prevent the occurrence of one when they were administered before and during the induction of the attack:

Histamine phosphate, 1:100,000 intravenously in dosages up to 10 c.c. (0.1 mg.) per minute; *acetylcholine hydrobromide,* 1:50, intravenously in dosages up to 3 c.c. (60 mg.), per minute; *sodium nitrite* by mouth in successive doses of 3 and 2 grains fifteen minutes apart.

Epinephrine, 5 c.c. of 1:30,000 (0.16 mg.) injected into the right antecubital artery in from two to three minutes. Following this there was an intense constrictor effect over the whole forearm and hand, with pallor lasting about fifteen minutes to be replaced by intense blushing. At this stage a typical attack was produced by immersion in cold water.

One dose of 25 million killed typhoid bacilli intravenously was followed by a chill and febrile reaction. Immediately following this,

when the hand was immersed in the usual manner, it was pink but cold, and remained so for twenty-five minutes, after which it gradually became cyanotic and then normal. Subsequently, spontaneous attacks occurred with their usual frequency.

DISCUSSION

It is known that in the clinical course of arterial hypertension or of arteriosclerosis certain vascular areas may become irritable, leading to attacks of spasm. Such spasm is claimed to play a rôle in the precipitation of cerebral crises, periodic cranial nerve palsies, angina pectoris, abdominal crises, intermittent claudications, and other clinical manifestations. The finer mechanism of these regional vascular disturbances is not known, for they have been but incompletely studied. The syndrome presented by this patient is of the same type of vascular disorder. The vessels of the fingers, and presumably of the toes, exhibited a vasospastic tendency. The fact that the cold had to be applied locally to exert its effect and that ulnar anesthesia did not influence the attacks, suggests that the irritability lies in the arterial wall itself and not in the nervous tissue. The finding that histamine and acetylcholine not only did not improve the attacks but failed even to prevent them, also suggests that the morbid changes were located in the vessel wall proper. The vasospastic tendency of the vessels was intense, for administration of sodium nitrite and typhoid bacilli, powerful dilators acting on the muscular coat, did not influence the attack.

The observations of empty capillaries or capillaries open and filled with stagnating blood and of low skin temperature indicate that the vascular occlusion must have developed proximal to the capillaries, in the arterial vessels, i.e., in small arteries or arterioles or in both. The fact that the induced venous stasis and dependent position of the arm had no appreciable effect on the pale color and coldness of the fingers indicates that the small venules were also in a state of active constriction. We have presented evidence that the venules of the skin are sensitive to chemical stimuli.[1]

Some of the observations, including the critical temperature for the precipitation of attacks, are in harmony with those described by Lewis on patients with Raynaud's disease.[2] While the classical Raynaud's disease appears in youth or in early adult life and emotions may play an important rôle, in the case studied and in others observed by us, this syndrome develops in late middle life or in old age after arterial hypertension has existed for several years. Whether arterial hypertension leads directly to irritability of the arterial vessels of the fingers or toes, or whether such a vasospastic tendency is the result of degenerative changes of these vessels secondary to arterial hypertension cannot be stated from this study.

SUMMARY AND CONCLUSIONS

1. Raynaud's syndrome precipitated by cold or by work occurs in patients with arterial hypertension and with arteriosclerosis.

2. Study of a case with severe attacks revealed that the clinical manifestations were due to an irritable and vasospastic state of the small arteries and arterioles of the fingers. The venules were also in spasm during attacks.

3. Vasodilator substances, such as histamine, acetylcholine, sodium nitrite, and typhoid vaccine, failed to prevent or alter the induced attacks, even when administered in doses sufficiently large to insure their maximum systemic effect.

4. Bright red "arterial" skin color may be associated either with very rapid capillary blood flow and normal tissue metabolism, or with sudden stagnation of blood flow and unusually low tissue metabolism.

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THE CIRCULATION TIME IN VARIOUS CLINICAL CONDITIONS DETERMINED BY THE USE OF SODIUM DEHYDROCHOLATE*

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INTRODUCTION

THE velocity of blood flow or, measured inversely, the circulation time has interested investigators for the past century. A review of the earlier work and a discussion of the principles involved are found in the very comprehensive papers of Blumgart[1] and Kisch.[2] Accurate methods applicable to man have been evolved only in the past decade.

The blood velocity may be measured as the distance covered by a particle of blood in a fixed interval of time, or, inversely, as the time elapsing to complete a known distance. From an experimental point of view it has been simpler to measure the time rather than the distance. The methods applicable to man, with any degree of accuracy, depend upon the rapid injection of a substance in an arm vein and its detection at some distant fixed point through properties depending upon the substance's color,[3, 4, 5] vasodilator effect,[6] neuromuscular stimulation,[7, 8] radioactivity,[9] or taste.[10] The time elapsing from the moment of injection to that of detection is known as the circulation time. When the method used involves primarily the blood flow through the lungs, a rough measurement of the pulmonary circulation time is obtained.

The simplest procedure was that devised by Bornstein[11] in 1912. He caused his patients to breathe a mixture of air with 5 to 7 per cent of carbon dioxide. As soon as the arterial blood carried the increased amount of carbon dioxide to the respiratory center, there followed an increase in the depth of respiration. The time elapsing between the start of the experiment and the onset of deeper breathing was regarded by Bornstein as half a circulation. The source of error in this method must be quite obvious when applied to patients with dyspnea, a condition in which the value of the blood velocity is of great interest.

In 1922 Koch[3] injected 1.6 per cent solution of fluorescin into one cubital vein, and collected samples of blood every five seconds from the other vein. The moment of appearance of the fluorescin deter-

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mined the circulation time. The technical difficulties were the inability to detect faint traces of fluorescin, to sample the blood at second intervals and the two venipunctures. Despite these drawbacks, the general behavior of the blood circulation time in normal and pathological states was rather accurately determined by him.

A similar method but utilizing Congo-red was reported by Klein and Heineman[4] in 1929. It suffers from very much the same objections as does the fluorescin method.

In 1922 Hirschsohn and Mandel[7] suggested the use of calcium chloride intravenously for determining the circulation time. They injected rapidly 5 c.c. of a 10 per cent solution. A feeling of warmth and a sensation of burning in the throat indicated the arrival of the drug at the neuromuscular junction. They were particularly interested in the effect of pneumothorax upon the blood velocity through the lungs.

Kahler,[8] using the same technic, repeated and amplified the above mentioned work in 1930. His results agree fairly well with those found by other methods. The normal values are more sharply delineated from the pathological than is possible with the dye method. Its drawbacks are the danger of slough and thrombosis from the rapid injection of calcium chloride if leakage occurs about the vein, the failure of some patients to respond, and the possibility of affecting the blood velocity itself by the use of calcium chloride.

In 1927 Blumgart and Yens[9] introduced their radium method, and for the first time it was possible to determine the circulation time from the site of injection to the right heart and the time from this point through the lungs, to the other arm. It is the introduction of a method of measurement of the pulmonary circulation time by Blumgart and his coworker that has proved of importance. This time tends to be a constant for a particular individual in the basal state. Variations from this value occur with exercise, drugs, and in anemia, polycythemia, emphysema, congestive heart failure, myxedema and hyperthyroidism. The time bears little or no relationship to weight, height, blood pressure, or pulse rate of the individual tested. Unfortunately, the method is so technical in its execution that it is not generally applicable.

In 1928 Weiss, Robb and Blumgart[12] used the intravenous injection of 1 mg. of histamine for the determination of the blood velocity. The circulation time was that required for the appearance of a reddening of the face and a metallic taste in the mouth. The serious drawback of this method is the severity of the reaction to histamine in some patients. It is scarcely suitable for the very sick. Confirmation of their results is found in the work of Wolheim[13] and Sebastiani.[14] Winternitz, Deutsch and Brill[10] found that if the histamine is diluted and a larger amount of fluid thus injected, a much shorter time is obtained in normal individuals than that found by Weiss and others. Seckel[15]

was able to use the histamine method in infants in whom the anterior fontanelle was still open, by injection into the longitudinal sinus through the fontanelle.

A rather complicated procedure which measured the change in volume of an extremity after the injection of an acetylcholine preparation was published in 1929 by Prusik.[6]

In a series of studies on the choleretic action of bile salts, Neubauer[16, 17] introduced the use of sodium dehydrocholate. It is readily soluble in water and oxidizes slowly in air. Its solution has a bitter taste and is slightly alkaline. The substance was found to be practically the only bile salt that could be injected intravenously without deleterious effect. A disagreeable side action was the intensely bitter taste that followed the injection of even small amounts. Winternitz, Deutsch and Brill[19] utilized this very property of the drug for the determination of the circulation time.

They injected 5 c.c. of a 20 per cent solution of sodium dehydrocholate (decholin) very rapidly (time not mentioned), and determined the moment of appearance of the bitter taste. The sensation was very transitory, lasting ten to twenty seconds, so that the test could be repeated with the needle remaining in the vein. There were no undue subjective sensations except occasional nausea. It apparently had little or no effect on the circulation itself. No alteration of the pulse rate was noted after the administration of the drug. They reported the results of over 700 injections without any complications.

It is this last method that we employed in the examination of our patients. We wish to call attention to its simplicity, and to the information which the determination of the circulation time may yield in the appropriate case.*

PROCEDURE

Although a constant amount of 5 c.c. of a 20 per cent solution of sodium dehydrocholate† was recommended by the original authors of the method, we found that an accurate response could be obtained in some patients with as little as 3 c.c. In general the faster the circulation time the less substance is needed to produce the taste. To avoid an intense reaction in patients suspected of having a very rapid time, the smaller amount may be used. In normal individuals or patients with heart disease, it is advisable to use only 5 c.c. In nearly 600 tests with 400 subjects there was always a positive response.

The test is usually performed in the morning, without breakfast, and under resting conditions. The subject lies as nearly flat in bed as possible. The arm is held at the level of the auricles. To avoid undue constriction the tourniquet is only applied just before the injection. The patient is instructed that he will experience a transient bitter taste in the mouth and tongue and is to respond at once when he perceives it. The injection is made rapidly with an 18 gauge needle

*The authors wish to acknowledge their indebtedness to Dr. Hermann Blumgart who first called their attention to this reference during a lecture on the blood velocity delivered at the Montefiore Hospital in 1931.

†The sodium dehydrocholate, known commercially as decholin sodium, was used by us.

and a 5 or 10 c.c. syringe. A stop watch records the time from the moment of injection to the arrival of the bitter taste. From 1 to 2 seconds are required for the injection. The time at the start of the injection rather than at the conclusion is taken, since the response may come with a minimum amount of the drug. The taste reaction persists for about 10 to 20 seconds. The patient's attention can be distracted from any unpleasant feeling afterwards by having him breathe deeply for half a minute. Occasionally there is a feeling of nausea shortly after the taste. In four instances, among all those tested, vomiting occurred as well. The nausea does not last more than a minute or two and is of no consequence. About 1 per cent of the patients tested also complained of pain in the right upper quadrant shortly after the injection. This may be due to sudden gall bladder distention.[18] There is no danger of slough or thrombosis from paravenous infiltration. The test may be repeated as soon as desired. Most of the cases reported are the results of two or more tests on the same patient. Cooperation on the part of the patient is necessary to secure an accurate response. The test is not reliable when the subject is in stuporous condition or mentally confused or has a loss of taste in the tongue. When in doubt about the accuracy of the response, it is advisable to repeat the injection.

In a number of patients we have checked the time through the use of calcium gluconate. This substance produces a feeling of heat in the mouth and over the body similar to that caused by calcium chloride. We have found the values, by the two methods, in the same patient to be the same, within the experimental error.

The subjects studied were all at the Mount Sinai or Montefiore Hospitals or were followed from the former institution to the latter. The group with heart disease is taken almost entirely from the Montefiore Hospital, that with diseases of the thyroid gland is chiefly from the Mount Sinai Hospital and the Radiotherapy Clinic* of the Montefiore Hospital. The results from both institutions have been combined in the charts and tables.

NORMAL INDIVIDUALS

Thirty normal men and thirty normal women, chiefly of the hospital staff, were tested. Their ages ranged from nineteen to fifty-eight years. The average circulation time was 13 seconds for the group of sixty. The extremes at rest were from 10 to 16 seconds. These normal values agree closely with the results reported by Winternitz, Deutsch and Brill.[10] Their upper limit of normal is set at 14 seconds, but they fail to include the time taken for the injection, which itself is usually one to two seconds. The sharpness of these normal time periods stands in contrast to the wider fluctuation found by the radium[1] and histamine[12] methods. That the results as reported by the last procedure are too high is indicated in the work of Winternitz, Deutsch and Brill previously quoted. It seems reasonable to assume that if the velocity of blood flow is not affected by the injected substance itself, the more rapid the time obtained under basal conditions, the more nearly accurate and absolute it is.

It is important to remember that exercise and excitement tend to shorten the circulation time. Under the same conditions there has

*We wish to thank Dr. M. Lenz and Dr. J. Fried for their kindness and cooperation in the study of these patients.

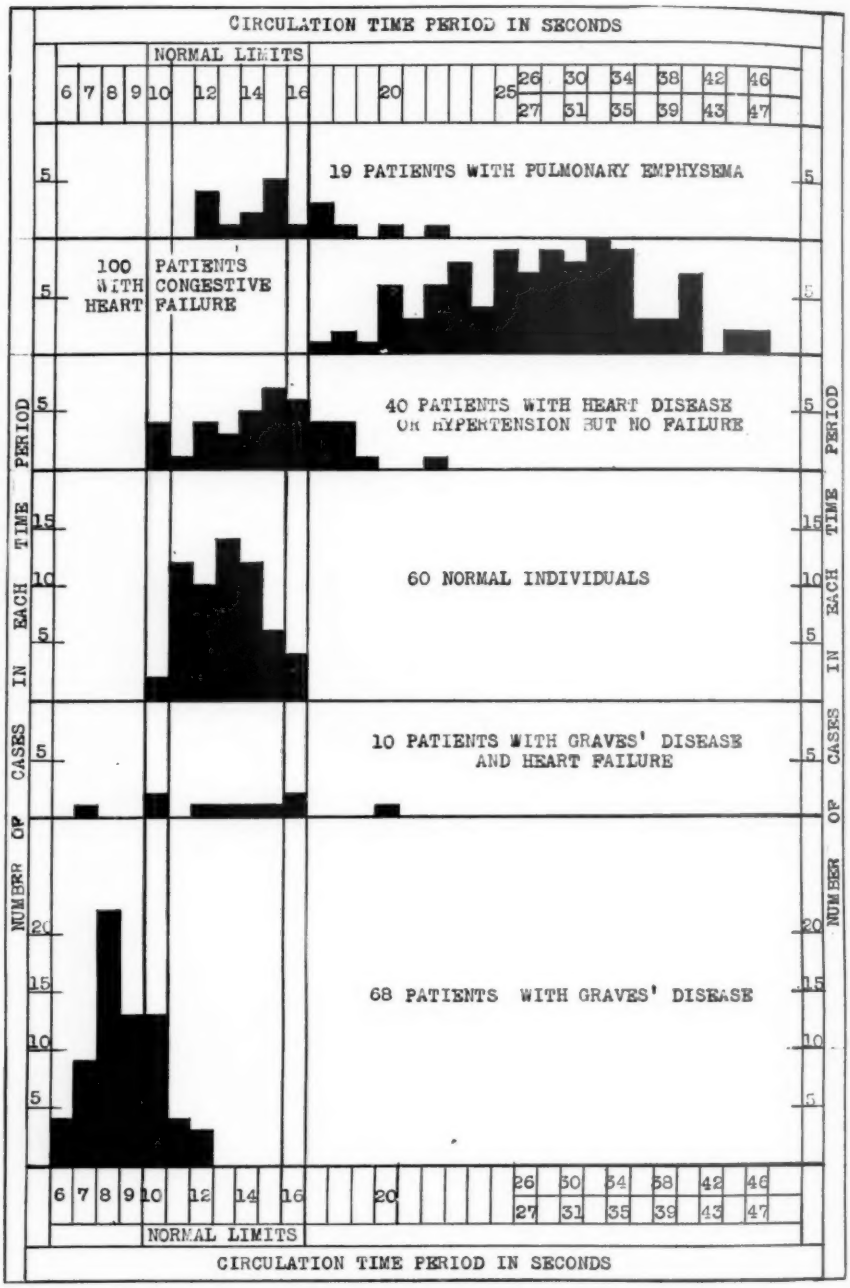

Fig. 1.—The blood circulation time in several clinical conditions.

been a remarkable agreement for the same subject. Duplicate values did not exceed 3 seconds' difference among the normal individuals.

Our data have been prepared in graphic form. Previous investigators have shown that in normal adults, the circulation time bears little or no relationship to weight, height, pulse rate and blood pressure. Our results agree with these findings. To avoid a confusion of figures, the height, weight, pulse rate and blood pressure have been omitted in the chart (Fig. 1).

HEART DISEASE

Congestive Heart Failure—Adults. Although Koch's studies[3] were limited to five-second samples, he was able to prove a definite slowing of the blood stream in congestive heart failure. His observations have been confirmed by all subsequent investigators. Except in the work of Kahler[8] and Winternitz, Deutsch and Brill[10] it has not been possible to deal with absolute values since the wide range of the normal by the fluorescin, radium and histamine methods also covered a certain percentage of the prolonged values found in congestive heart failure. It is quite probable that all the last three methods yield absolute values which are too high.

In the report of Kahler[8] it is to be noted that periods above 17 seconds are found chiefly in patients with signs or symptoms of congestive heart failure.

Winternitz, Deutsch and Brill[10] set the limit of normal at 14 seconds but fail to state whether this was exclusive of the time required for injection, which itself may be 2 seconds. They likewise found prolonged time periods chiefly in patients with congestive heart failure. Blumgart[1] averaged the different groups and found the time periods of those with congestive heart failure considerably above normal.

Since there can be no sharp clinical differentiation of patients with circulatory failure from those who are just on the borderline but rather only a gradual merging of one group into another, it is to be expected that the circulation times will reflect a similar condition. In so far as it was clinically possible we have attempted to separate a group of 140 adult patients with hypertensive, arteriosclerotic, rheumatic and syphilitic heart disease into those with and those without congestive heart failure. The patients were observed for periods of time varying from weeks to months. As evidence of congestive failure in a patient with a known cardiac lesion we used the presence of (1) dyspnea, (2) pulmonary congestion on physical or x-ray examination, (3) enlargement of the liver, (4) edema, and (5) ascites. We feel justified in making the diagnosis in the presence of the first three criteria alone and at times in the presence of only the first two. In 100 patients of the 140, congestive heart failure was diagnosed. In 92 of the 100, the liver was palpably enlarged, and in 47 edema was

TABLE I

CIRCULATION TIME IN CHILDREN WITH HEART DISEASE

NAME	DATE	AGE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
Group 1. Rheumatic Heart Disease Without Signs of Congestive Heart Failure							
K. R. ♂	11/18/31	13	83	80	108/80	13 sec.	Chronic rheumatic cardiovalvular disease, mitral stenosis and insufficiency, chorea.
	12/ 9/31		83	100		12 sec.	Clinical condition unchanged.
P. F. ♀	12/11/31	13	95	116	80/40	13 sec.	C. R. C. V. D.,* mitral stenosis and insufficiency, transient auricular fibrillation.
S. L. ♂	2/ 8/32	12.5	75	60	110/65	12 sec.	C. R. C. V. D., aortic stenosis and insufficiency.
	3/11/32		76	84		12 sec.	Condition as above.
S. C. ♂	1/ 6/32	13	100	92	130/0	17 sec.	C. R. C. V. D., aortic insufficiency, mitral stenosis and insufficiency.
	2/16/32		100	78	128/0	15 sec.	Clinical condition unchanged.
F. A. ♂	12/ 9/31	12	70		128/0	10 sec.	C. R. C. V. D., aortic insufficiency, mitral stenosis and insufficiency, secondary anemia; 3,650,000 R.B.C., 70% hg.
S. H. ♂	10/ 1/32	12	64	104	120/80	11.5 sec.	C. R. C. V. D., mitral stenosis and insufficiency.
Group 2. Congestive Heart Failure in Rheumatic Fever							
S. G. ♂	12/ 3/31	11	43	104	120/20	17.5 sec.	C. R. C. V. D., aortic insufficiency, mitral stenosis and insufficiency, fever; liver enlarged, pulmonary congestion, pericarditis. Very apprehensive.
E. K. ♂	11/20/31	10	53	120	120/50	17 sec.	C. R. C. V. D., aortic insufficiency and stenosis, pericarditis, fever; edema present, liver enlarged. Died one week later.
Group 3. Congestive Heart Failure Dominates the Clinical Picture							
W. A. ♂	11/18/31	11	77	110	110/50	35 sec.	C. R. C. V. D., aortic insufficiency, mitral stenosis and insufficiency; liver enlarged, edema of lower extremities present.
	11/20/31		77.5	100		29 sec.	Clinical condition unchanged.
	12/ 8/31		72	100	108/50	28 sec.	Lost 5 pounds of edema fluid after salyrgan injection; condition otherwise the same.
S. T. ♂	11/18/31	11	78	84	90/60	38 sec.	C. R. C. V. D., mitral stenosis and insufficiency, auricular fibrillation, liver enlarged, edema present.

TABLE I—CONT'D

NAME	DATE	AGE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
			Group 3—Cont'd				
S. T. ♂	12/ 9/31		70	80	92/60	23 sec.	Has lost 8 pounds of edema fluid on salyrgan and digitalis therapy; much improved; liver edge still at previous level, no edema.
	1/ 6/32		70	80		24 sec.	Clinical condition as noted on 12/9/31.
N. R. ♀	12/11/31	13	84	118	124/0	23 sec.	C. R. C. V. D., aortic insufficiency; liver enlarged.
	1/12/32		85	105		21 sec.	Clinical condition unchanged.
I. K. ♀	12/11/31	11	59	120	80/40	24 sec.	C. R. C. V. D., mitral stenosis and insufficiency; liver enlarged.
	1/12/32		62	100		21 sec.	Clinical condition unchanged.
R. L. ♀	12/16/31	14	120	84	110/30	40 sec.	C. R. C. V. D., mitral stenosis and insufficiency, auricular fibrillation; liver enlarged, edema present.
	1/ 6/32		111	80		45 sec.	Has lost 9 pounds of edema fluid; improved clinically.
R. T. ♀	3/ 2/32	15	58.5	100-120	90/60	25 sec.	C. R. C. V. D., mitral stenosis and insufficiency, acute pleurisy; liver enlarged; temperature 101.8°.
	4/ 4/32		62	180	95/65	27.5 sec.	Onset of paroxysmal tachycardia that lasted 1½ hours at time of circulation test. Only complaint was palpitation.
	5/ 6/32			110	92/60	25 sec.	Feels better than on admission; liver still enlarged.
	10/20/32			90	100/60	30 sec.	Auricular fibrillation has lasted for 10 days, rapid ventricular rate at start —154 per minute, now controlled by digitalis. Clinically patient feels worse; congestive heart failure present.
	10/25/32			87	110/65	28 sec.	Regular rhythm restored following quinidine; clinically improved; congestive heart failure still present.
			Group 4. Borderline Congestive Heart Failure and Rheumatic Fever				
J. P. ♂	12/ 9/31	12	57	120	110/68	16 sec.	C. R. C. V. D., mitral stenosis and insufficiency. On borderline of congestive failure.
	2/ 5/32		59.5	100		19.5 sec.	Clinical condition somewhat worse than on admission; liver edge just palpable.

TABLE I—CONT'D

NAME	DATE	AGE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
			Group 4—Cont'd				
	5/ 6/32		58	112	102/60	14 sec.	Respiratory infection, coughing. Liver edge 2 fingers below costal border.
	6/29/32		64	104		14 sec.	Clinical condition good; liver not palpable.
	10/ 1/32		66	104	105/60	15 sec.	No fever; clinical condition good; liver edge barely palpable.

*C. R. C. V. D. — Chronic rheumatic cardiovalvular disease.

present. The other 40, although suffering from complaints referable to the cardiovascular system could not be considered as belonging to the first group. Their complaints were either precordial pain, dyspnea, or weakness without accompanying signs of pulmonary or hepatic congestion or edema of cardiac origin.

Every one of the 100 patients with clinical congestive heart failure had a circulation time that was more than 17 seconds. In 96 of the 100 the time was 20 seconds or more and ranged up to 47 seconds. The other group of 40 without congestive failure contained all grades from those who barely showed any cardiac involvement to those who were on the verge of failure. Yet of this group, in only 10 was the circulation time 17 seconds or more. Nine of these 10 periods were between 17 and 19 seconds and the tenth one was 21 seconds. The general average of the group without congestive failure is about 2 seconds higher than normal. The general average of the group with congestive failure was 26 seconds, or 13 seconds above the normal average.

Congestive Heart Failure—Children. The blood velocity of 15 children with chronic rheumatic cardiovalvular disease was investigated. Their ages ranged from ten to fourteen years. Technical difficulties and the possibility of an inaccurate response precluded the use of younger children. Between 3 and 5 c.c. of sodium dehydrocholate were injected, depending upon the age and clinical condition of the patient (Table I).

In 6 of the 15 children there was no evidence of congestive heart failure. Clinically they suffered more from the effects of rheumatic fever than from a failing circulation. As the table indicates, undoubted valvular lesion was present in each one. The average circulation time for this group was 13 seconds, with the extremes at 12 and 17 seconds. We have had no opportunity of determining the circulation time in normal children and but little data are available in the literature. In two patients, eight and eleven years of age admitted for surgical treatment without any cardiac complications, the circu-

lation time was 10 seconds in each. We believe that the circulation should not be much different from that in adults.

In two of the 15 children congestive heart failure occurred during the course of a severe rheumatic pancarditis. The patients were critically ill, and one died several days after the test was performed. The circulation time was 17 seconds in each case. The enlargement of the liver and the signs of pulmonary congestion lead one to assume a fairly severe grade of cardiac failure. The time of 17 seconds appears rather short and may be the result of the active rheumatic fever.

In six of the children the signs and symptoms of congestive heart failure outweighed the manifestations of the rheumatic activity. The circulation time for this group was from 21 to 45 seconds. Although the number of cases is small, they would appear to behave very similar to the adult group.

One patient, J. P. (Table I), was on the borderline of congestive heart failure clinically. His circulation time fluctuated on five occasions from 14 to 19.5 seconds. As the table indicates, the shortest time was obtained during the course of a respiratory infection. There was no elevation in temperature accompanying it.

Miscellaneous Cardiac Conditions—Congenital heart disease. One patient with a congenital heart lesion, diagnosed as a stenosis of the pulmonary artery and an overriding aorta, had on three occasions circulation time periods of 11, 7.5 and 9.5 seconds. There were marked cyanosis and dyspnea present but there was no evidence of congestive heart failure. The rapid time of 7.5 seconds is suggestive of a venous arterial shunt in the heart, whereby a part of the circulating blood is pumped directly to the tongue without passing through the lungs.

Subacute Bacterial Endocarditis. Of four patients with subacute bacterial endocarditis engrafted upon rheumatic valvular disease, two showed normal circulation time periods. One, with a marked secondary anemia and elevated temperature had a time of 9 seconds. The fourth case had a circulation time of 27 seconds and presented undoubted clinical evidence of congestive heart failure and auricular fibrillation. Despite the severity of the pathological process in the heart, circulation time periods within normal limits were found in those patients who showed no evidence of congestive heart failure.

Pericardial Tumor. One patient with a pericardial tumor which invaded the auricle and clinically led to congestive heart failure had a circulation time of 20.5 seconds, in keeping with what was expected. The diagnosis was confirmed at the post-mortem examination.

Cardiac Asthma. We were able to determine the blood velocity in two patients during attacks of paroxysmal cardiac dyspnea that simulated bronchial asthma. Both patients suffered from arteriosclerotic heart disease and had evidence of mild congestive heart failure. The circu-

TABLE II

VARIATIONS IN THE CIRCULATION TIME WITH CHANGES IN THE CLINICAL CONDITION OF THE PATIENT

NAME AGE SEX	DATE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
E. W. 52 years ♀	11/27/31	93	100	140/100	38 sec.	Hypertension and coronary artery disease. Bundle-branch block. Edema and ascites present.
	1/ 6/32	111	84	130/90	54 sec.	Has gained 18 pounds of edema fluid; clinically much worse.
	2/ 5/32	109	86	135/90	43 sec.	Edema and ascites still present.
	3/18/32	109	88	145/96	48 sec.	Edema and ascites still present.
	5/11/32	109	100		45 sec.	Edema and ascites still present.
H. R. 57 years ♂	11/18/31	135	76	110/70	27 sec.	Coronary artery disease. Auricular fibrillation. Edema and ascites present.
	11/25/31	126	70		33 sec.	Slight improvement due to loss of 9 pounds of edema fluid with digitalis and salyrgan.
	12/ 2/31	120	84	106/68	33 sec.	Continues to lose edema fluid; no ascites present.
	12/15/31	123.5	90		25 sec.	Very much improved; no edema present.
	1/ 7/32	127	92	112/70	35 sec.	Still in congestive heart failure, but no edema or ascites.
A. G. 71 years ♂	11/20/31	125	92	96/75	43 sec.	Hypertension, coronary artery disease, auricular fibrillation. Edema, ascites, hydrothorax.
	12/16/31	114	70		28 sec.	Loss of 11 pounds of edema fluid. Ascites and hydrothorax cleared up.
	12/18/31	115	80	110/80	26 sec.	Continues to improve clinically. Edema absent.
	1/27/32	122	84		25 sec.	State of nutrition better. Edema absent.
	2/ 8/32	125	90	100/70	26 sec.	State of nutrition better. Edema absent. Liver still enlarged.
	3/21/32	119	72		32 sec.	Returned in congestive failure after leaving the hospital. Edema, ascites present.
A. B. 54 years ♀	12/ 2/31	120	88	182/100	16 sec.	Hypertensive heart disease, pulmonary congestion. Liver edge barely palpable.
	12/16/31	123	84	185/100	18 sec.	Has gained 3 pounds of edema fluid. Congestive failure more pronounced.
	12/21/31	121	112	180/90	22 sec.	Respiratory infection; fluids forced; liver edge now 2 fingers below the costal border; temperature 100°.

TABLE II—CONT'D

NAME AGE SEX	DATE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
C. T. 56 years ♂	11/25/31	110	42	230/60-80	25 sec.	Coronary artery disease, complete heart-block, congestive heart failure with edema.
	1/ 6/32	107	46	210/80	35 sec.	General condition worse; edema of lower extremities pronounced.
	2/ 8/32	107	36	220/90	34 sec.	Condition the same for past month.
	3/ 2/32	104	34	204/84	35 sec.	Slight change in physical status.
	5/ 6/32	107	72	160/70	20 sec.	Spontaneous restoration to sinus rhythm. Subjectively and objectively very little change.
	5/ 8/32	106	38	180/80	37 sec.	Reversion to heart-block after 3 days; feels worse; no changes objectively.

TABLE III

CIRCULATION TIME IN POLYCYTHEMIA

NAME	AGE	TOTAL RED BLOOD COUNT	HEMOGLOBIN	TOTAL BLOOD VOLUME	VOLUME PER KILOGRAM	CIRCULATION TIME	BLOOD PRESSURE	DIAGNOSIS
A. M. ♂	50	6,250,000	120%	5,220 c.c.	87 c.c.	16.5 sec.	130/80	Secondary polycythemia. Duodenal ulcer.
J. C. ♂	28	7,600,000	125%	6,190 c.c.	113 c.c.	16.5 sec.	106/76	Polycythemia vera.
J. A. ♀	34	9,350,000	154%	3,300 c.c.	193 c.c.	18.5 sec.	126/88	Polycythemia vera.
S. D. ♀	56	8,500,000	137%	6,900 c.c.	133 c.c.	18 sec.	184/96	Polycythemia hypertonica.

lation time periods were found prolonged but not radically different from the time periods between the episodes of dyspnea.

Tachycardia and Bradycardia. In two patients we had the opportunity of determining the effect of marked fluctuation in the pulse rate on the circulation time. One was a child, R. T. (Table I), who had chronic rheumatic cardiovalvular disease with congestive failure. She was subject to attacks of paroxysmal tachycardia (demonstrated by the electrocardiogram). Her complaint at such times was chiefly cardiac palpitation. The episode began and ended suddenly and lasted from several minutes to several hours. As the table shows, the circulation time remained practically the same during an attack that lasted one and one-half hours in which the usual rate of 100 to 120 had risen to 180 beats per minute.

The other patient, C. T. (Table II), suffered from arteriosclerotic heart disease with complete heart-block. His past history showed that on several occasions he had established a regular sinus rhythm with a pulse rate up to 84 per minute, instead of his usual rate of 38 to 46 per minute during block. Such changes were spontaneous, lasted several days, and were not accompanied by subjective or objective improvement in the clinical condition. The patient's basic circulation time during the four months prior to his latest episode of sinus rhythm was 35, 34, and 35 seconds, with his rate fluctuating from 34 to 46 per minute. Examined on the third day of a period of sinus rhythm with a rate of 72, the circulation time was found to be 20 seconds. Two days later the rate was 38 and the circulation time had returned to its previous level—37 seconds. For five days the patient had had a sinus rhythm, demonstrated by numerous electrocardiographic tracings. There had been little or no change objectively or subjectively in his clinical condition. Congestive failure continued as before; yet the velocity of blood flow had almost doubled. Significant as well is the drop in blood pressure that occurred at the same time (see Table II).

Comment. With the exception of one patient with heart-block, described in Table II, no constant relationship was found between the blood pressure, venous pressure, pulse rates, or weight of the patient and the circulation time. While there is a tendency for the time to be prolonged in proportion to the degree of congestive heart failure, there were exceptions to this as well, especially in the presence of active rheumatic fever. As improvement occurred with digitalis and diuretic therapy, the time was generally shortened. In those who improved sufficiently as no longer to be classified in congestive failure, the time tended to return to the upper limit of normal. However, the correlation was not so exact as to make the test of prognostic value.

Nearly all those who showed prolonged times were tested twice. Whereas in the normal the duplicate tests under the same conditions showed a maximum difference of plus or minus 3 seconds, those with prolonged time showed fluctuations up to 8 seconds, especially in the group with periods above 30 seconds. Similarly, the deviation from the general average of 13 seconds in the normal was plus or minus 3 seconds, whereas in the group with congestive heart failure it was minus 9 seconds to plus 24 seconds. It was rather a surprising clinical demonstration in many cases to obtain repeated circulation times in the same patient agreeing to one second.

DISEASES INVOLVING THE LUNGS AND PLEURA

Pulmonary Emphysema. The difficulty of accurately diagnosing cardiac failure in the presence of pulmonary emphysema is well recognized clinically. The cardinal symptoms of dyspnea, cyanosis and cough are present in both conditions.

Blumgart and Weiss[19] found the circulation time in 21 out of 25 patients with pulmonary emphysema to be within normal limits. "The normal or even increased velocity of blood flow particularly in those patients who had many of the symptoms and signs of severe circulatory failure such as conspicuous weakness, cyanosis and dyspnea is of great importance. It shows that pulmonary emphysema alone is sufficient for the production of these symptoms and signs." (Blumgart.)

Of a total of 19 patients with pulmonary emphysema either idiopathic in origin or secondary to a long-standing asthma, bronchitis or fibroid tuberculosis, normal circulation time periods were found in 13 patients. In one of these there was clinical evidence of congestive heart failure. In the remaining six patients there was a slight prolongation of the circulation time—up to 22 seconds. In four of these six patients there was clinical evidence of congestive heart failure, either secondary to right heart involvement or upon an independent basis.

Pneumonia, Tuberculosis. Hirschsohn and Mandel,[7] using calcium chloride, showed that the blood velocity in pulmonary tuberculosis is within normal limits and is not affected by the volume of the lung. Pneumothorax, apparently, has little effect upon the velocity of the circulation through the lung. We examined a group of 9 patients with pulmonary disease in whom we were certain that no cardiac complications existed. Four of these patients had at the time a lobar or bronchopneumonia accompanied by elevation in pulse, temperature and respiratory rates. The other five patients suffered from active pulmonary tuberculosis.* The circulation time period for the group ranged from 7.5 to 13.5 seconds and the average time was 11.2 seconds.

In two patients with pulmonary tuberculosis in whom evidence of congestive heart failure was found during life and at necropsy, the circulation time was beyond 20 seconds.

In the presence of the increased metabolic rate accompanying fever it seems reasonable to expect an increased blood velocity. The general average for the group is nearly 2 seconds faster than normal. In evaluating congestive heart failure in such a group it would be safe to accept time periods between 16 and 20 seconds as suspicious of cardiac involvement.

POLYCYTHEMIA AND MYXEDEMA

The only other conditions that may produce a slowing of the blood velocity or a prolongation of the circulation time are polycythemia[1] and myxedema.[1] In six patients with polycythemia observed by us the time was prolonged. In two of these there was undoubted evi-

*These five patients were seen through the courtesy of Dr. Maurice Fishberg on the Tuberculosis Division.

dence of severe coronary artery disease, so that it was not possible to place the responsibility upon the polycythemia alone. In the other four there was no evidence of cardiac failure. The relationship of the polycythemia to the circulation time in the other four patients is shown in Table III. The time periods begin at the upper limit of normal and run to 18.5 seconds. The prolongation is not very striking; yet it is in keeping with the altered physiology of the blood movement in polycythemia.

One patient with myxedema was observed before treatment. Her basal metabolic rate was minus 32 per cent, pulse 70, hemoglobin 70 per cent, red blood count 3,700,000, and the circulation time 21 seconds. After the administration of 44 grains of thyroid, the patient showed evidence of overdosage. Excitement was present, the temperature was elevated to 100.4° F., pulse was 84 per minute, the basal metabolic rate was minus 10 per cent, and the circulation time 8 seconds. Another patient had a circulation time of 16.5 seconds with a basal metabolic rate of minus 36 per cent. Following thyroid therapy, the basal metabolic rate rose to minus 6 per cent and the circulation time decreased to 13 seconds.

GRAVES' DISEASE

Blumgart, Gargill and Gilligan[20] were the first to measure the blood velocity in patients with thyrotoxicosis. In 13 patients they found an increased speed of blood flow through the lungs that was 85 per cent faster than the average normal. They were able to relate the rapid time to the elevation in the basal metabolism. It appeared to be an almost linear function of the latter. With a reduction in basal metabolic rate to normal the circulation time approached the normal.

Kahler[8] reported the results of 6 tests on the same number of patients. The times ranged from 7 to 12 seconds; the average of the group was definitely faster than the normal.

We were able to perform 100 tests of the blood velocity on 78 patients who suffered from Graves' disease and in whom the basal metabolic rate was elevated from plus 5 per cent to plus 87 per cent. Of these 78 patients, 10 had at the time of measurement evidence of cardiac failure, as a possible result, either of the thyrotoxicosis, or of a coincidental cardiac lesion. The average circulation time for the group of 68 without cardiac failure was 9 seconds in contrast to the normal of 13 seconds. The individual times ranged from 6.5 to 12 seconds. The circulation times of the patients with cardiac failure ranged from 6.5 to 19 seconds and averaged 13 seconds. These times bear out the findings of Blumgart, Gargill and Gilligan.[19] For the degree of cardiac failure present one would have expected a much more prolonged time for the group, at least 20 seconds. The circula-

tion time period in patients with congestive heart failure and Graves' disease seems to be an arithmetical average of what would be expected in either condition alone. Through the measurement of the circulation time it was possible to recognize two cases of Graves' disease which at first impression had been clinically masked by symptoms of a coincidental rheumatic heart disease.

In four patients with enlargement of the thyroid gland due to adenomata and not associated with evidence of hyperthyroidism, the circulation time periods were 10.5, 12, 12, and 14 seconds.

In four patients with neurocirculatory asthenia whose complaints were very similar to those of patients with hyperthyroidism, but whose basal metabolic rates were normal, the circulation time periods were from 10 to 12.5 seconds. Further studies in this group are contemplated. No conclusion can be drawn from so small a number of cases.

An attempt to relate the circulation time to the elevation in the pulse rate in the patients with Graves' disease was not successful. Neither have we been able to relate as closely as Blumgart did, the increased blood velocity to the elevation in the basal metabolic rate. In general we found that those with the highest basal metabolic rate and the fastest pulse rate had the shorter times, but, likewise, times of 8 seconds were found in patients whose metabolic rate was only 16 per cent above normal and who clinically had active Graves' disease. In the performance of the test on patients with hyperthyroidism complete cooperation is absolutely essential for an accurate result. Unless the test is done with the patient completely at rest, a shorter time than is normal for that patient will be obtained. Blumgart has pointed out that in addition the variable factor of arm to heart time may be responsible for the failure to correlate the data.[1]

ANEMIA

The consensus of opinion regarding the dynamics of the circulation in severe anemia is that the cardiac output per minute tends to increase and the velocity of blood flow with it. Such a mechanism is one of the means of supplying the requisite amount of oxygen to the tissues when a deficiency of hemoglobin exists. The other mechanism is more complete utilization of the arterial supply of oxygen with a resultant greater arteriovenous oxygen difference.

In a study of 18 patients with severe anemia, both primary and secondary, in none of whom symptoms of cardiac failure existed so far as could be determined clinically, the average circulation time was 12 seconds. The individual values fluctuated from 9 to 15 seconds. The average in our series of 60 normal controls was 13 seconds, with fluctuations from 10 to 16 seconds. The difference is not very striking, but no conclusions can be drawn from so small a group.

MISCELLANEOUS CLINICAL CONDITIONS

It was of interest to investigate the circulation time in a group of diseases in which enlargement of the liver, edema, ascites, or dyspnea might raise the question of circulatory failure in the differential diagnosis. Such conditions are chronic glomerulonephritis, the nephroses, cirrhosis of the liver, the obscure group of hepatosplenomegalies, and occasionally neoplasms.

Cirrhosis of the Liver. In 9 patients with hepatic enlargement due to cirrhosis, amyloidosis, or hemochromatosis, despite the occasional presence of marked ascites, the circulation time was normal. In 2 patients with a hepatosplenomegaly of unknown etiology and normal blood findings, the circulation time was likewise normal.

Carcinoma and Sarcoma. In 16 patients with carcinoma or sarcoma involving different abdominal organs and accompanied in some by secondary anemia, the circulation time was 10 to 15 seconds.

Nephritis. In glomerulonephritis the blood velocity was investigated by Koch[3] and Kahler[8] and found to be more rapid than normal. This is due to the secondary anemia usually seen in those patients. We examined 13 patients whose clinical picture was primarily renal in origin.

In 5 patients with chronic glomerulonephritis with and without edema, the circulation time was 11 to 14 seconds. There was no evidence of congestive heart failure in any of the five. Moderate to severe anemia, hypertension, cardiac hypertrophy and dilatation were present in all.

In 4 patients with renal insufficiency, either due to glomerulonephritis or arteriosclerosis and complicated by congestive heart failure, the circulation time was prolonged beyond 20 seconds in two and at 16 and 17 seconds in the other two patients. There was a severe secondary anemia present in all of them. Those with times above 20 seconds died within a short time after the test. At autopsy there was confirmation of the congestive failure. Whether the time in any individual patient is prolonged beyond 20 seconds depends upon the degree of heart failure and the admixture of anemia.

Normal circulation times were found in one patient with marked hypertension and renal insufficiency due to uric acid calculi, in two patients with amyloid nephrosis, and in one with a combination of diabetes mellitus, nutritional edema and renal insufficiency due to calculi.

EFFECT OF EXERCISE AND NONBASAL STATES

Strictly basal conditions such as twelve hours fasting and one hour absolute rest were only adhered to in about 50 per cent of our cases investigated. We were more interested in securing the usual value with the subject at rest. The slight difference that occurs between

the strictly basal and the resting states we found to fall within the limit of the experimental error. In patients with congestive heart failure Kahler[8] found that even moderate exercise did not affect the circulation time materially. These patients are already working with their maximal cardiac reserve. They are unable to meet the demands for increased work on the part of the circulation.

In five normal subjects who were examined by us during a period of moderate activity, such as routine floor nursing, the circulation time was found to be at the faster level of normal in three. In the two others the time periods were as rapid as 8 seconds. Kahler[8] reported shortening of the circulation time from 1 to 4 seconds in normal individuals after moderate exercise.

The importance of maintaining basal conditions is indicated in the patients suspected of Graves' disease. The circulation time of an apprehensive, nervous patient without hyperthyroidism may be as rapid as one with a markedly elevated basal metabolic rate.

DISCUSSION

The condition of greatest clinical importance in which a slowing of the blood stream occurs is congestive heart failure. Here it is independent of the etiological factor, whether rheumatism, hypertension, arteriosclerosis, or syphilis. Auricular fibrillation, when present, influenced the circulation time in our cases only in so far as it was associated with congestive heart failure. The significance of a prolonged circulation time from a teleological point of view is beyond the scope of this communication. Clinically, it is of importance in the differential diagnosis of cardiac failure from conditions simulating it. Excepting one case with heart failure in the course of pulmonary emphysema, a prolonged circulation time was found in every patient with edema of cardiac origin. Conversely, a normal time in the presence of undoubted clinical cardiac failure should make one search for factors which would tend to increase the velocity of blood flow. The most usual are hyperthyroidism, fever and severe anemia. Similarly, in clinical hyperthyroidism a normal or prolonged circulation time should lend suspicion to early cardiac failure.

In 92 per cent of our patients with congestive heart failure enlargement of the liver was present on palpation. In all these the circulation time was prolonged beyond normal limits. Conversely, enlargement of the liver accompanied by a normal circulation time in heart disease has led us to investigate for a possible hyperthyroidism, or an independent cause for the liver enlargement. In two of our patients with hypertension and enlarged liver, congestive heart failure was suspected because of the large liver. A normal circulation time led to a more careful review of the history and revealed a cirrhosis of the liver as the responsible factor for the hepatic enlargement.

The recognition of cardiac failure in the presence of one or two other clinical conditions such as nephritis, amyloid nephrosis, tuberculosis, cirrhosis of the liver, and starvation edema is sometimes a difficult clinical problem. If the failure has progressed to a degree responsible for liver enlargement or edema, the circulation time will be found prolonged.

In congestive heart failure accompanying or caused by pulmonary emphysema a comparatively slight diminution of the blood velocity was noted by Blumgart.[1] Our patients showed similar findings. No satisfactory explanation for this phenomenon can be offered at present.

SUMMARY

1. The several methods proposed for the determination of the velocity of blood flow or circulation time and the results obtained are reviewed.

2. A simple procedure utilizing the injection of sodium dehydrocholate (decholin-sodium) is outlined for performing the test. The precautions to be observed are discussed.

3. The average circulation time in normal resting adults for the blood to travel from the arm vein, through the heart and lungs, and up to the mouth, is 13 seconds, as determined by sodium dehydrocholate. The normal range is 10 to 16 seconds.

4. The blood velocity was determined in 140 adult patients with heart disease due either to hypertension, arteriosclerosis, rheumatic fever, or syphilis. In so far as it was possible clinically, they were divided into two groups: those without and those with manifestations of congestive heart failure.

(a) There were 40 patients in the group without cardiac failure. The circulation time in 30 of these was within normal limits. In the remaining 10 patients the time was between 17 and 21 seconds. The general average for the group was 15 seconds, only 2 seconds above the average for normal adults.

(b) There were 100 patients in the group with signs of congestive heart failure. In 96 of these 100 patients the circulation time was 20 seconds or more and ranged up to 47 seconds. In only 4 of the patients was the circulation time less than 20 seconds. It was not less than 17 seconds in any of the four. The general average for the group was 26 seconds—twice the average for normal adults.

5. The blood velocity of a group of 15 children with rheumatic heart disease was investigated. Their general behavior was similar to that of adults. Active rheumatic fever tended to increase the blood velocity in two of these children in whom congestive heart failure was also present.

6. The blood velocity was determined in patients with such different cardiac conditions as congenital heart disease, subacute bacterial endo-

carditis, paroxysmal cardiac dyspnea, pericardial tumor, paroxysmal tachycardia, and heart-block. Its significance in these conditions is discussed.

7. Caution must be exercised in interpreting the values for the circulation time in patients suspected of having heart failure in the presence of pulmonary emphysema or marked pulmonary fibrosis.

8. Fever and anemia tend to increase the velocity of blood flow.

9. A slowing of the blood velocity was found in patients suffering from polycythemia or myxedema.

10. The blood velocity was determined in 78 patients with clinical manifestations of Graves' disease. They were divided into two groups: those without and those with evidence of heart failure.

(a) In 68 patients who showed no evidence of heart failure the blood velocity was distinctly faster than normal. The average for the group was 9 seconds and the extremes ranged from 6.5 to 12 seconds.

(b) In 10 patients with signs of cardiac failure in addition to the Graves' disease, the circulation time tended to be an arithmetic average of the two conditions. The average for the group was 13 seconds.

11. Through determination of the blood velocity, the possibility of recognizing congestive heart failure in the presence of such different clinical entities as cirrhosis of the liver, carcinoma, Bright's disease, and hyperthyroidism is indicated.

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CONGENITAL ANOMALIES OF THE CORONARY ARTERIES: REPORT OF AN UNUSUAL CASE ASSOCIATED WITH CARDIAC HYPERTROPHY*

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DEVELOPMENTAL defects of the coronary arteries unassociated with co-existing congenital anomalies of the heart or great vessels are of interest because of their infrequent occurrence and the possibility of their serious significance.

In 6,800 post-mortem examinations during the past 37 years at the Massachusetts General Hospital anomalies of the coronary arteries of sufficient extent to warrant mention in the anatomical diagnosis of the cases have been noted in only 4 instances. Except in the case herewith recorded, the remaining abnormalities were incidental post-mortem findings of no clinical importance in three adult male patients; one consisted of a small accessory right coronary artery, the second comprised a single normal-sized coronary artery, the left, which gave rise shortly after its origin to a branch which followed the course usually taken by the absent right coronary artery, and in a third instance the right coronary was much smaller than normal with its circumflex branch extending only 2 cm. from its origin, whereas the size and distribution of the circumflex branch of the left coronary artery in contrast were considerably larger than normal.

Significant abnormalities of origin where one of the major coronaries arises from the pulmonary artery are important in that extensive degenerative changes in the myocardium may result from the inadequate blood supplied to the region involved; or, if the patient survives to adult life, which is exceptional, curious dilated and tortuous arterio-venous aneurysms may develop upon the heart wall. We are reporting a case recently encountered at the Massachusetts General Hospital which presented the rare combination of a left coronary artery of normal size arising from the pulmonary conus co-existent with an otherwise unexplained hypertrophy of the heart as a whole, together with degenerative changes in the wall of the ventricle largely confined to the area supplied by this malposed vessel.

*From the Cardiac Clinic of the Massachusetts General Hospital, Boston, Mass.
Read at the annual meeting of the International Association of Medical Museums, Washington, D. C., May 8, 1933.

We have encountered in the literature only eight cases where one or other of the main coronary arteries, usually the left, arose from the pulmonary artery, and a few additional cases in which an accessory third coronary had a similar origin. A review of the reported cases reveals features of unusual interest which will be commented upon later.

CASE REPORT

A three-months-old male infant weighing 11 pounds was admitted to the hospital on July 26, 1932, because of recurring attacks of dyspnea, pallor, and profuse sweating for the preceding two weeks. Delivery had been entirely normal and at term. Both parents as well as an older brother two years of age are normal.

Nothing remarkable was noted about the patient until the tenth week; while nursing from the bottle the onset of an unusual group of symptoms occurred which

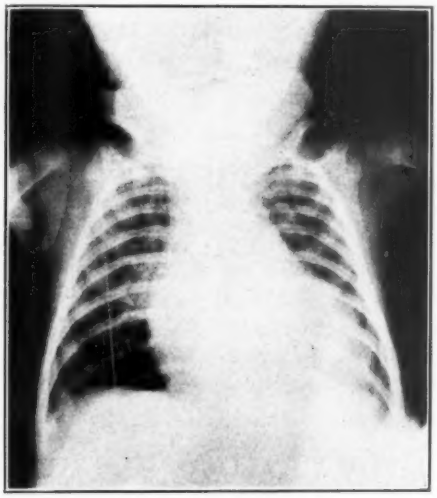

Fig. 1.—An x-ray film of the chest showing the diffuse cardiac enlargement which was most prominent in the region of the ventricles. The tube distance in this instance was seven feet from the heart.

consisted of paroxysmal attacks of acute discomfort precipitated by the exertion of nursing. The infant appeared at first to be in obvious distress as indicated by short inspiratory grunts, followed immediately by marked pallor and cold sweat with the general appearance of severe shock. Occasionally with unusually severe attacks there appeared to be a transient loss of consciousness. The eructation of gas at times seemed to relieve the discomfort and to shorten the duration of an attack, which usually lasted from five to ten minutes, and following which the infant might proceed to nurse without difficulty and remain free of symptoms for several days. It is noteworthy that during the above seizures cyanosis was not an outstanding sign, but appeared only when the infant cried vigorously, and even then was not pronounced. The lungs remained free of congestion and there was no significant change in the rate or rhythm of the heart. Convulsions never occurred even during the transient periods of apparent unconsciousness. These observations were first made by the infant's father who is himself a physician and a very careful observer, and were confirmed by one of us.

The attacks increased in severity and the child was admitted to the hospital for study. X-ray films of the chest taken before hospitalization revealed diffuse cardiac enlargement chiefly in the region of the ventricles. This finding was confirmed by films taken after admission (Fig. 1). In the hospital the child appeared to be essentially a normal infant, and the only abnormal finding on physical examination was a definite increase in the area of cardiac dullness. No murmurs were audible, and no clubbing of the fingers or constant cyanosis was noted. The electrocardiogram showed normal axis deviation, but well marked inversion of the T-waves in all leads, of the coronary type (late inversion) (Fig. 2). We considered this change in the T-wave significant especially in that no digitalis or other drug had been administered. Low voltage of the QRS complexes was also present.

During observation in the hospital the child appeared to be doing well. Slight pallor was present at times after nursing or crying. On August 9, 1932, he had a severe attack of difficult respiration with expiratory grunts and for the first time

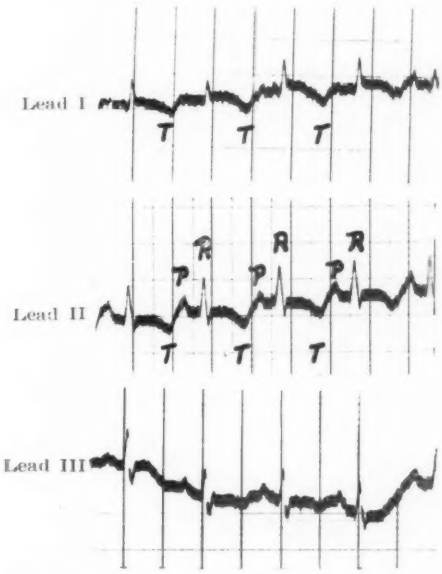

Fig. 2.—An electrocardiogram showing a late and deep inversion of the T-wave of the coronary type especially well shown in Leads I and II. Time interval is 0.2 second.

marked cyanosis. He was placed in an oxygen tent without significant improvement. Death occurred eighteen hours later apparently from respiratory failure. The clinical diagnosis was congenital idiopathic hypertrophy of the heart.

Necropsy.—A post-mortem examination performed twelve hours after death revealed the following findings: The thymus was normal. The liver extended 6 cm. below the xiphoid and 4 cm. below the costal margin. It weighed 185 grams (normal 140 grams). The kidneys were normal. The left lung was moderately collapsed as a result of pressure from the enlarged heart.

The heart weighed 91 grams (normal 25 grams). The left ventricular wall measured 11 mm. and the right 3 mm. in thickness. The chamber of the left ventricle (Fig. 3) was large and its wall occupied the entire apex of the heart, whereas the right ventricle (Fig. 4) was relatively smaller than normal with its tip 2 cm. from the apex. All of the valves were normal—thin and sufficient—with circumferences as follows: mitral 4.4 cm., aortic 2.4 cm., tricuspid 5.0 cm., and the

pulmonic 2.3 cm. The right coronary artery (Figs. 3 and 5) arose at its usual site from the aorta by one large mouth and an adjacent small mouth, the latter supplying branches to the upper portion of the right ventricle. The larger mouth communicated with a normal-sized right coronary which coursed along the auriculo-ventricular groove giving off anterior branches to the right ventricle and a large posterior descending branch which occupied the posterior sulcus between the right and left ventricles and continued almost to the apex (Fig. 5). The main right coronary artery continued in a horizontal direction to a point where the inferior vena cava entered the right auricle, and in this region bent downward to fade out over the wall of the left ventricle posteriorly. The left coronary artery, normal in size, arose from the pulmonary artery (Figs. 4 and 5). A few millimeters from its mouth it divided in a Y-shaped fashion. The larger branch coursed downward over the apex, then curved backward and upward on the posterior aspect of the left ventricle, and gradually faded into the muscle wall. The second branch was quite

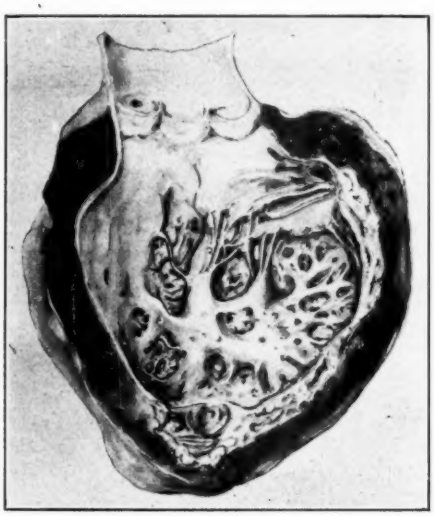

Fig. 3.

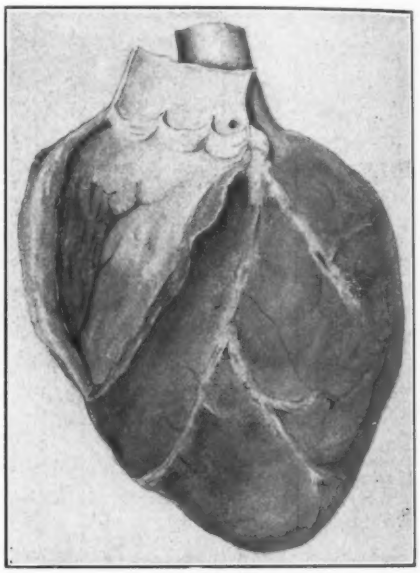

Fig. 4.

Fig. 3.—A drawing showing the well marked hypertrophy and dilatation of the left ventricle. The right coronary orifice is seen above the right aortic valve. (For this and subsequent drawings we are indebted to Miss Dorothy Norton.)

Fig. 4.—Showing the relatively small size of the opened right ventricle. The orifice of the left coronary artery is seen above the left pulmonary cusp.

small and supplied the upper part of the left ventricle. The inferior vena cava at its point of entry into the right auricle also communicated with the left auricle by a narrow slitlike opening 3 mm. in length. The ductus arteriosus was slightly patent at the aortic end, but was completely occluded as it approached the pulmonary artery.

The microscopic examination of the tissues was made by Dr. Tracy B. Mallory.

The greatly increased thickness of the heart wall was due in part to an increase in the number of muscle fibers, and in part to the separation of the muscle bundles by unusually large spaces, the result of vascular dilatation together with a small amount of fibrosis between the bundles. The average width of the muscle fibers was no greater than that of a control section from an infant nine weeks of age. Sections taken from the wall of the right and of the left ventricle showed

no appreciable differences in the size of the muscle fibers. However, on the endocardial surface of the left ventricular wall there was marked fibrous thickening with occasional patches of fibrosis at deeper levels. A considerable proportion of the muscle cells showed two and three nuclei in close proximity or even in contiguous chain formation, strongly suggestive of the chains of nuclei seen in degenerating skeletal muscle attributed to amitotic nuclear division. Careful search failed to reveal mitotic figures. In a few areas groups of vacuolated muscle cells with large pale nuclei were seen, presumably "hydropic" degeneration since fat stains were negative.

The greater part of the lung sections showed markedly thickened alveolar walls. In some areas the lung tissue was not recognizable, the appearance being that of a mass of small darkly stained nuclei surrounded by thick fibrils and infiltrated with monocytes. In the center of one of the masses a small bronchiole could be seen. The arterioles were very thick and their lumina were almost obliterated.

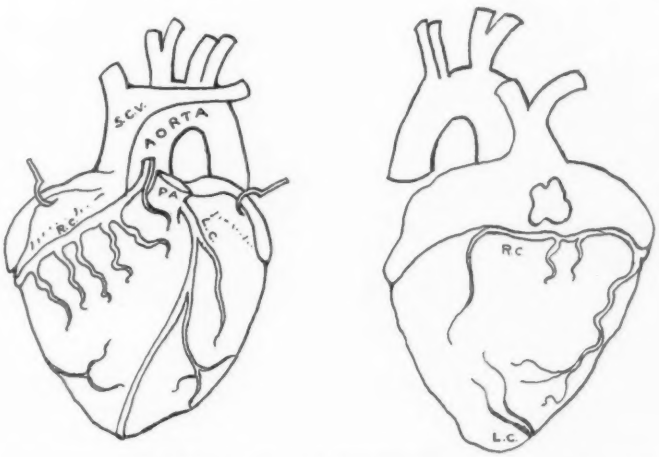

Fig. 5.—Drawings showing the origin and distribution of the right and left coronary arteries, the latter arising from the pulmonary artery.

The kidney sections were normal. The liver showed marked vacuolization and a moderate destruction of cells.

The anatomical diagnosis was congenital cardiac hypertrophy, congenital anomalies of the coronary arteries and the inferior vena cava, and fibrosis of the endocardium of the left ventricle.

DEVELOPMENTAL ANOMALIES OF THE CORONARY ARTERIES

Although little is known concerning the development of the coronary vessels in the human embryo, presumably it is similar to that which takes place in other mammals. According to Martin[31] the first anlage of the future coronary artery in rabbits is a club-shaped bud which makes its appearance from the endothelial surface of the bulbus arteriosus about the twelfth day of embryonic life and before this common trunk has been divided by the so-called spiral septum into the aorta and pulmonary artery. Lewis[20] states that the coronary bud appears nearer the fourteenth day. The anlage for the

left coronary artery is first formed, and somewhat later that for the right makes its appearance. Grant[14] has more recently reviewed the entire subject and states that "indications of the coronary arteries appear as thickenings of the aortic endothelium in embryos (rabbits) of 10-11 mm. greatest length. Here again, there is some variation. In this series an endothelial bud corresponding to the left artery is seen in specimens of 10, 11, 11.5 mm. in length; in another specimen of 11 mm. no arterial bud is to be found, but both right and left buds are present in a second 11.5 mm. embryo. Figure 7 shows the commencement of the right coronary in a 11.5 mm. embryo—the stage

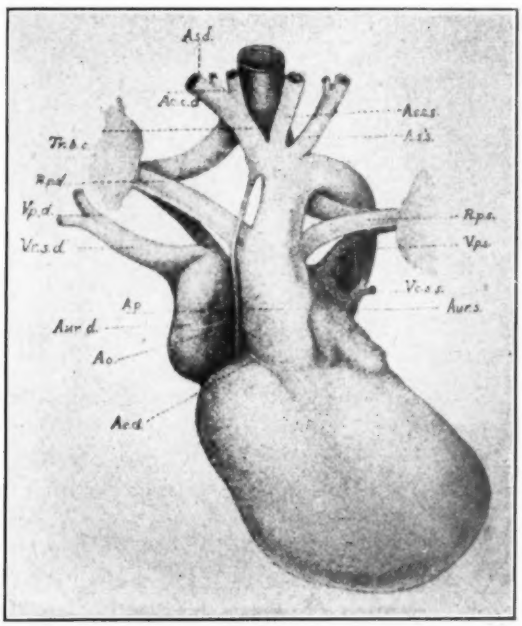

Fig. 6.—After Konstantinowitsch, showing the origin of the right coronary artery from a rudimentary aorta (Ao). The origin of the left coronary from the pulmonary artery is not shown in the diagram. (Prag. med. Wchnschr. 1906.)

at which the truncus communis is being separated into aorta and pulmonary artery by the growth of the endothelial cushions. The arterial rudiments are first solid columns of cells which later acquire a lumen and grow outward into the superficial portion of the myocardium."

Congenital abnormalities of the coronary vessels may exist as isolated pathological curiosities of no clinical significance; as such they usually remain entirely unsuspected until discovered in the course of a post-mortem examination. True anomalies of the coronaries are not commonly associated with extensive developmental defects in the heart or great vessels other than transposition of the great trunks or

situs inversus of the heart. Occasionally the coronary anomaly itself may be of considerable importance and its relationship to certain cases of congenital hypertrophy of the heart is of interest. The observed cases of variation in the coronary vessels are sufficiently infrequent and yet important enough to warrant a brief review of the subject. They may be grouped under two main headings: (a) Abnormalities of origin; (b) Variations in number, size, and distribution.

Abnormalities of Origin.—The origin of one of the major coronary stems from the pulmonary artery unassociated with other significant developmental defects is rare. We have encountered reports of only 8 cases in addition to the one we are recording of this unusual arrangement. It is obvious that because of the extensive co-existent vascular defects the cases recorded by Konstantinowitsch and Dreyfuss which are to be commented upon later do not properly belong in this small group. In 1911 Abrikosoff[2] reported the first case in a five-and-one-half-months-old infant who died of pneumonia. Autopsy revealed well marked cardiac enlargement due in part to an aneurysmal dilatation of the left ventricle. The right coronary arose in the usual place, but the left took origin from behind the left leaflet of the pulmonary artery from an ostium that was slightly wider than normal. The vessel divided and had the usual distribution of an otherwise normal left coronary artery. The anterior wall of the left ventricle near the apex was completely replaced by a transparent fibrous tissue membrane of only 0.5 mm. thickness in its central portion and which extended over an area about 2 cm. in diameter. Small areas of calcification were present and the vessels to this part showed a definite endarteritis, but without obliteration of the lumina, which was interpreted as being a process coincident with, rather than a possible cause of the myocardial degeneration. It was further noteworthy that the fibrous tissue replacement of the wall was maximal in the region supplied by the descending ramus where anastomotic connections with the right coronary artery are minimal. There were no other congenital defects present. The case of Heitzmann[19] (1916) was identical and occurred in a three-and-one-half-months-old female infant who died with cyanosis and syncope. Here, again, the right coronary was normal, but the left arose in the left sinus of Valsalva of the pulmonary artery. There were marked fibrosis and thinning of the wall of the left ventricle as well as of the anterior papillary muscles; the latter contained areas of calcification. A diffuse endocardial thickening of the septum and marked aneurysmal dilatation of the left ventricle were present as well as enlargement of the heart as a whole. The author was impressed by the striking similarity of this picture to that observed in older people with myocardial infarction and fibrous tissue replacement resulting in aneurysmal dilatation of

the wall, and dependent upon preceding coronary sclerosis and occlusion. Kiyokawa's patient[24] lived four months. The clinical course was identical with ours in that for the first few weeks the child was entirely normal. Death occurred after several weeks during which frequent attacks of dyspnea, cyanosis, and convulsions occurred. The heart was greatly enlarged, and the wall of the left ventricle supplied by the anomalous left coronary was reduced to a thickness of 1 mm. The endocardium of the left ventricle showed the usual marked hyperplasia.

The remaining cases have not shown such marked degrees of myocardial fibrosis, but here again the degenerative changes have been of a similar nature. The case recorded by Scholte[41] of a two-and-one-half-months-old female who died of bronchopneumonia showed post mortem well marked cardiac enlargement. The right coronary artery arose at its normal site, but the left sprang from the left sinus of the pulmonary artery. There was marked fibrosis of the myocardium of the left ventricular wall, together with fatty degeneration of the muscle fibers, areas of necrosis and calcification, and a diffuse thickening of the endocardium of the left ventricle. It is of interest that the most extensive changes here occurred nearer the endothelial than the pericardial surface of the ventricular wall, a situation analogous in some respects to that observed after coronary occlusion where the area of infarction is usually of greatest extent near the endothelial surface and dependent, no doubt, upon the relatively scant vascular supply and anastomotic connections of this portion of the wall. The patient of Carrington and Krumbhaar[6] lived twelve months. The heart showed well marked hypertrophy and no gross difference in the appearance of the two ventricles. The left coronary arose from the pulmonary artery just above the posterior cusp and nourished much less than half of the heart, a fact which perhaps accounted for the relative longevity of the case. In sections from the area supplied by the malposed vessel there was a distinct increase of interstitial fibrous tissue, rather diffuse and here again more marked near the endocardial section of the wall. The parenchymatous degeneration (loss of striae and vacuolization) was also most marked in the areas supplied by the anomalous artery, the walls and lumen of which were normal. In discussing the etiology of the congenital hypertrophy in this case the authors felt that the rôle of the abnormal coronary and the myocardial fibrosis, though thought by them unimportant, must be considered as possible etiological factors. Stevenson's instance (cited by Abbott)[45] is similar and occurred in a three-months-old infant; the excessive hypertrophy and dilatation of the left chambers were extensive enough to produce atelectasis of the lung, hoarseness, and difficulty in passing a feeding tube.

In exceptional instances patients have attained adult age in spite of this apparently serious variation in the coronary vessels, and in striking contrast to the cases noted above is the picture presented by Abbott's remarkable patient,[1] a woman aged sixty-four years who died accidentally. Gross hypertrophy and extensive fibrosis of the myocardium were present. The right coronary arose in the usual place by a much dilated orifice and expanded directly into a huge thick-walled loop the size of a crab apple which projected 2.5 cm. above the subepicardial fat. Descending branches as well as the main trunk of the vessel were wide thick-walled tortuous channels. No coronary arose from the usual site of the left, but instead a large patulous opening lay in the floor of the dilated posterior sinus of Valsalva of the pulmonary artery and from this opening sprang a large thin-walled trunk of venous character which divided 1 cm. beyond into two large branches which followed in general the course of the branches of a normal left coronary. The descending branch expanded into a large triangular shaped sinus 2 cm. in diameter at its widest portion. In the floor of this sinus were several thick-walled septa behind which large vessels opened into it from the myocardium, strongly suggesting that the course of the blood was toward the pulmonary artery, a view also shared by Brooks[5] who had previously encountered two cases in which an accessory coronary vessel arose from the pulmonary artery and meeting the branches from the two aortic coronaries produced a remarkable anastomosis of a circoid character. A case mentioned by Krause[26] is in some respects analogous; and more recently Feriz[10] has recorded similar instances. In this particular accessory coronary group the extra vessel is relatively small and probably of no importance in the nourishment of the heart, since it seems likely that the direction of the blood flow in the anomalous vessel is toward the pulmonary artery. Finally, the eighth case, that mentioned by Schley,[40] is unique in that it is the only instance where the malposed vessel originating from the pulmonary artery was the right coronary; furthermore, there was no evidence of a reversal of flow and aneurysm formation or of myocardial fibrosis. The patient was a sixty-one-year-old laborer who died with auricular fibrillation and congestive failure. At autopsy there was evidence of cardiovascular lues; insufficiency of the aortic leaflets, aortitis, and aneurysmal dilatation of the ascending aorta. The right coronary arose above the right valve of the pulmonary artery. The left coronary artery arose at its normal site but supplied a larger portion of the heart than is usual. There were no gross anastomoses between the two vessels. A careful histological examination of the wall of the two ventricles showed no alterations such as have been noted in the other seven recorded cases, and there was no evidence that the abnor-

mal coronary had either handicapped or shortened this man's life even though portions of the myocardium must have been nourished in part by insufficiently aërated blood.

There appear to be two possible explanations to account for this interesting variation in the origin of one or other of the coronary arteries. The most likely background for this anomaly, as has been pointed out by others, would seem to be a faulty arrangement of the primitive endothelial buds before the division of the truncus arteriosus has occurred, so that one or the other is misplaced to the portion of the common trunk destined to become the pulmonary artery. On the other hand, although the *anlagen* of the coronary vessels may be in their proper place, the position taken by the spiral septum may be at fault, the division taking place too far to the right, thereby including one of the coronary buds in the pulmonary portion of the dividing trunk. Support is lent to this last hypothesis by the case of Konstantinowitsch where the division of the truncus arteriosus was obviously abnormal.

Minor variations in origin of the coronary arteries, usually from a higher level in the aorta, are not infrequently encountered and when unassociated with other defects are unimportant. Giepel[13] records a case in which the right coronary artery arose from the ascending aorta 7 mm. above the cusp margins. Hyrtl[21] mentions an instance where the right artery arose near the origin of an abnormal artery thymica 16 mm. above the right aortic sinus, and in Schrader's case[42] the right coronary arose 18 mm. above the cusp margins of an otherwise normal heart. More extensive so-called misplacements have been noted where one or other coronary artery arises from the arch of the aorta, the innominate, or even from a carotid artery. Farre[9] in 1814 described a cor biloculare in a male infant of seventy-nine hours from whose ventricle arose a single arterial trunk which first gave off two large pulmonary branches and continued on to give origin to the innominate, the left carotid and the left subclavian arteries. It also sent downward a single artery to the heart wall which appeared to be its only coronary supply. The continuation of the main arterial trunk had the usual appearance of the descending aorta. Forster's case[11] is identical, and here again the abnormal vessel appeared to furnish the sole blood supply to the heart. In Jürgen's specimen,[22] the description of which is brief and inadequate, a right coronary artery is said to have arisen from the arch of the aorta. Somewhat analogous is the patient of Owen-Clark,[34] the case of the cor triloculare biatriatum of a two-and-one-half-day-old female infant, in which a single arterial trunk arising from the ventricle was entirely void of coronary connections at the normal sites, but gave off two pulmonary branches, a short innominate trunk from which the carotids and the

right subclavian took origin, as well as a small artery which descended to the interspace between the large arterial trunk and the right auricle having the appearance of a rudiment of the ascending aorta and furnishing the coronary arteries. The case of Vernon[48] is similar in that the point of origin was from the innominate. In the instance mentioned by Power-Heath (cited by Peacock[38]) the coronary artery was cut across but apparently arose from the aorta or one of its branches; whereas Pitschel[36] and Mayer[32] found the origin of a right coronary artery from the carotid artery, and in Tow's case[47] a single vessel from a pulmonary branch of the common arterial trunk was distributed to the heart and appeared to be its only source of blood supply.

Konstantinowitsch[25] appears to have been the first to suspect the true nature of the majority, and perhaps all, of the above cited cases, from Farre through Tow, of so-called high origin of a coronary artery; and furthermore, because of the important evidence furnished by his remarkable case as related to a possible explanation cited above of the abnormal origin of coronary vessels from the pulmonary artery, the description and diagram of his specimen is given. A two-day-old female infant dying with the signs of cyanosis and collapse showed at autopsy a cor biloculare with a rudimentary aorta, completely stenosed at its origin at the base of the ventricle, but giving rise to the right coronary artery, the blood to which passed down the patent stem of the rudimentary aorta from its connection with the innominate (Fig. 6). The left coronary artery arose from the large trunk designated the pulmonary artery. The author believed that here the misplaced origin of the left coronary was dependent upon the obviously abnormal division of the truncus arteriosus. Furthermore, attention was called to the fact that in the so-called "high origin" of the coronary artery of those cases where the aorta appears as a rudimentary vessel a similar interpretation may apply, so that instead of a true high origin the coronary actually arises at an approximately normal level from a rudimentary ascending aorta. This conception, shared by Rauchfuss[39] and also by Abbott[1] who has recorded a case of atresia of the ascending aorta with coronaries from the blind lower end, would indicate a single direction in these cases otherwise difficult to explain on a reasonable embryological basis; and would include further the cases recorded by Kussmal,[28] Taruffi[46] and Schrader[42] (an additional case, not the one already referred to). In the last mentioned case both coronaries were given off from the rudimentary aorta as separate vessels. Recently Dreyfuss[7] has described a case similar in many respects to that of Konstantinowitsch of a cor biventriculare triloculare in which there was stenosis of the rudimentary aorta. Here, also, the left coronary artery arose from the large pulmonary trunk.

Variation in Number, Size, or Distribution.—Less important anomalies in the arrangement of the coronary vessels are chiefly those involving a variation in number or distribution. Normally the coronaries arise from the right and left sinuses of Valsalva above the corresponding semilunar valves of the aorta. Rarely both arteries may arise from a single stem or from adjacent openings in the same sinus.[4, 8, 20, 35, 37, 43] Usually the primary branches from the single stem follow the customary course of the right and left arteries respectively, but in Plaut's case[37] as well as in that of Petrén,[35] there was no vessel found which from its position or direction could be considered a counterpart of the absent right coronary artery, and in the instance mentioned by Engelmann[8] only a small rudimentary vessel arising from the single large left coronary had any resemblance to the right vessel, but a large and entirely abnormal branch of the descending ramus coursed downward over the right ventricle nearer the apex than the auricle and appeared to be the chief supply to the right side of the heart. An interesting complication has been recorded by Smith and Graber[43] of a typical coronary thrombosis in a forty-six-year-old man who died of subsequent congestive failure. The blood supply to the entire heart was furnished by a single large artery which during its early course corresponded in location with that of the right coronary artery. Later branches were given off which resembled in a diminutive manner the descending and circumflex branches of the left coronary artery. The difference between the size of these vessels and that of the usual two main branches of the left coronary artery was striking. The blood supply to the left ventricle was thus apparently much less than in the normal subject, and it was difficult to understand how the blood supply in this instance permitted the individual to perform the heavy physical work to which he was accustomed.

More frequently the number of coronaries is increased to three and very rarely to four.[3, 5, 10, 12, 16, 17, 23, 26, 30, 33, 50] The accessory arteries are small and as a rule arise a short distance from the origin of one of the main coronary stems and in general are distributed along a course analogous to that of a branch of the main vessel, so that occasionally the circumflex branch of the left coronary arises as a separate vessel from the left sinus. In several cases already noted[5, 10, 26] the accessory vessel arose from the pulmonary artery. Krause in Henle's *Handbook of Anatomy*[20] mentions a compensatory widening of the distribution of one vessel associated with an unusual decrease in the size of the other. In the presence of complete atresia of the pulmonary orifice the coronaries may dilate and send anastomotic branches contributing to the collateral circulation through the lungs. In the interesting case cited by Voss[49] the patient reached the age of thirty-seven years in spite of a

completely closed pulmonary artery. An adequate collateral circulation to the lung was maintained chiefly by four bronchial arteries arising from the descending aorta and anastomosing with branches from both coronary arteries which pursued a tortuous course to be distributed to the circulation through the lungs. A curious variation of the coronary circulation occurred in Grant's case,[15] in which blood filled spaces in the right ventricular muscle formed a nodule 6 mm. in diameter and communicated freely with the cavity of the ventricle and with the coronary arteries and veins. The malformation was interpreted by the author as representing a persistence and growth of the intertrabecular spaces of the compact myocardium which are normally reduced to capillaries. Ingleby's case mentioned by Abbott[1] is analogous. A unique case was encountered by Halpert[18] as an incidental necropsy finding in a male adult and consisted of an arteriovenous communication between the right coronary artery and the coronary sinus with aneurysmal dilatation of the parts involved.

COMMENT

The structural alterations occurring in the heart wall of the small series of reported cases where one of the coronary arteries arises from the pulmonary artery are important and give rise, with the one exception noted,[40] to a characteristic pathological picture of well marked myocardial degeneration, in some cases even to the extent of complete fibrous tissue replacement in the region supplied by the anomalous artery, with resulting aneurysmal dilatation of the ventricular wall. In addition to the greater or lesser local changes, there is well marked hypertrophy of the heart as a whole which probably represents a compensatory mechanism. Death within the first year of life is the rule. One must assume, we believe, that these parenchymal changes are dependent in large part upon two factors: (1) the inadequate nourishment of the ventricular wall by *venous blood* and (2) the relatively low pressure in the coronary artery arising from the pulmonary artery. It is of interest further to note the striking similarity of the varying degrees of degenerative changes encountered in this series of cases to those arising as a result of an inadequate blood supply secondary to coronary sclerosis and narrowing in adults where one finds in the more advanced cases complete occlusion, myocardial infarction, and eventual fibrous tissue replacement of the wall. It is evidently of some clinical importance that in our case, which appears to have been the only one in which an electrocardiographic study was made, the tracing showed the unmistakable sign which we have come to associate with important coronary disease in adults; namely, a deep and late inversion of the T-wave in all three leads, together with the supportive evidence of low voltage of the QRS complexes. It is of interest that such was not the case in a recently reported instance of uncomplicated and idio-

pathic congenital hypertrophy in an infant seven months old whose electrocardiogram was normal in all respects.[44]

In retrospect when we consider the grossly abnormal and qualitatively inadequate blood supply of the left ventricular wall resulting in myocardial ischemia with subsequent degenerative changes, together with the electrocardiographic finding of a "coronary" type of T-wave, it seems probable that in this infant the curious attacks of paroxysmal discomfort, precipitated by exertion and accompanied by a profound reflex vasomotor disturbance, were those of angina pectoris. If this be true, it represents the earliest age at which this condition has been recorded. An explanation for the freedom from symptoms during the early weeks of life remains obscure. The necropsy finding of slight patency of the aortic end of the ductus botalli suggests the possibility that it may not have become occluded until several weeks after birth, thereby permitting the admixture of arterial with venous blood in the pulmonary artery, but of this we have no proof.

It is suggested that in future cases of uncomplicated and unexplained cardiac enlargement in infancy the finding of a similar electrocardiographic picture in the absence of abnormal axis deviation or toxemia may indicate an inadequate and anomalous coronary supply to the heart.

SUMMARY

An instance is recorded, in a male infant dying at the age of three months, of an abnormal origin of the left coronary artery from the pulmonary artery, associated with marked enlargement of the heart (due to hypertrophy and dilatation of the left ventricle), together with extensive degenerative changes in the ventricular wall supplied by the malposed vessel. In view of these findings, it is probable that the paroxysmal attacks of acute discomfort precipitated by exertion and associated with profound vasomotor collapse occurring in this infant were those of angina pectoris. The electrocardiographic picture in our case was similar to that seen in adults with important coronary disease. In the few recorded cases (8 in number in addition to our own) of this rare anomaly a characteristic pathological picture has resulted. Death within the first year has been the rule. Two of the cases have been exceptional.

A review of congenital variations in the coronary vessels and a discussion of their embryological background are included. A bibliography is appended.

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ANOMALOUS ORIGIN OF THE LEFT CIRCUMFLEX CORONARY ARTERY*†‡

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WITH increasing interest in and knowledge of the clinical and pathological picture of coronary artery disease, anatomical studies of the normal distribution and variations of the blood vessels of the heart are assuming greater significance than heretofore.

Variations in the coronary arteries may be considerable in reference to their origin, course, distribution and anastomoses. Anomalies of the coronary arteries may at times have clinical importance, as illustrated in the cases described by Abrikossoff,[1] Carrington and Krumbhaar[2] and Scholte[3] in which one of the two coronary arteries arose from the pulmonary artery. Death occurred in the early months of life due to myocardial failure associated with myocardial degeneration of that portion of the heart (left ventricle) supplied by the anomalous vessel.

NORMAL DISTRIBUTION OF THE MAIN CORONARY ARTERIES

A short résumé of the usual origin and distribution of the main coronary vessels will aid in the understanding of the anomaly to be described. The average normal human heart is supplied by two coronary arteries. The left coronary artery arises from the left sinus pocket of the aorta and divides about a half centimeter from its origin into two branches, an anterior descending and a circumflex branch. The right coronary artery arises from the right sinus pocket of the aorta and emerges between the roots of the pulmonary artery and aorta, pursuing its course to the right along the auriculoventricular sulcus up to and usually beyond the crux§ of the heart posteriorly. The terminal branches of the right coronary artery supply the posterior part of the right ventricle and part of the posterior portion of the left ventricle. (Fig. 1.)

ANOMALOUS CORONARY ARTERY

In the cases presented in this report, the right coronary artery and the left anterior descending branch of the left coronary artery of the

*From the Laboratories of the Mount Sinai Hospital, New York City.
†Presented before the New York Pathological Society, Dec. 23, 1929.
‡Aided by a grant from the Lucius N. Littauer fund.
§Crux: That situation of the heart posteriorly where the auricles and ventricles meet. (Gross.[4])

heart have their normal origin, course and distribution. The left coronary artery, however, does not give rise to the circumflex branch.

In three of the four cases studied, the left circumflex coronary artery takes its origin directly from the aorta in the right sinus pocket, just posterior to the mouth of the right coronary artery, and in one case from the main right coronary artery. The vessel equals in caliber that of the main coronary arteries. It proceeds backward and to the left for a short distance, between the root of the aorta and the right auricular

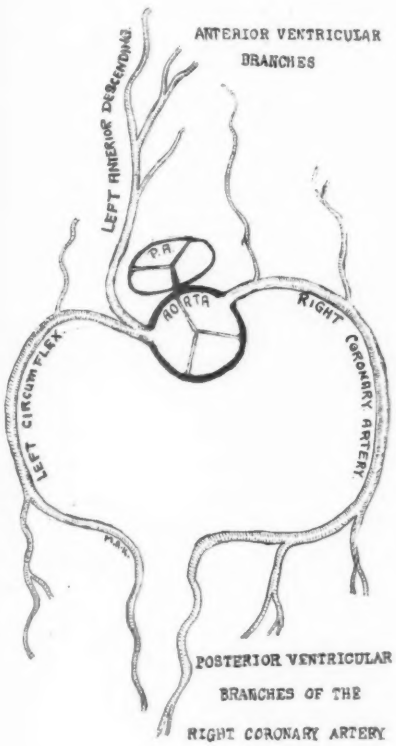

Fig. 1.

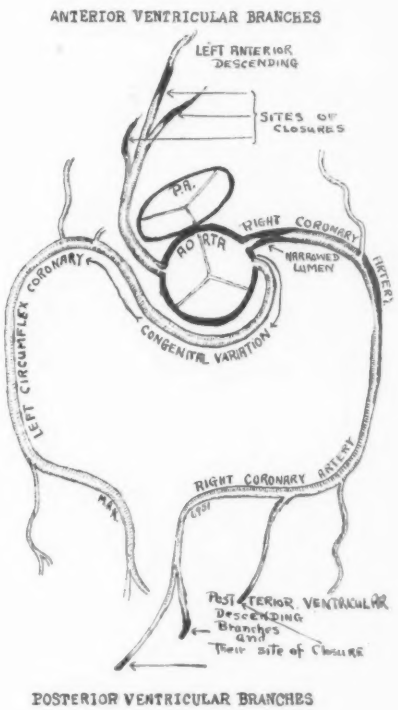

Fig. 2.

Fig. 1.—Diagram of normal origin and distribution of the main coronary arteries. The vessels are spread out on a flat plane.

Fig. 2.—Diagram showing origin and distribution of the left circumflex coronary artery in the case which presented multiple occlusions in the ramifications of the left anterior descending branch and in the posterior ventricular branches of the right coronary artery.

appendage, just above the interventricular septum, hugging closely the posterior portion of the aorta at its root. It then circles anteriorly to emerge between the root of the aorta and the left auricular appendage in the auriculoventricular sulcus of the left side, and for the rest of its course occupies the bed normally held by the left circumflex coronary artery. (Figs. 2, 3 and 4.)

ANASTOMOSES BETWEEN THE ANOMALOUS VESSEL AND THE OTHER CORONARY ARTERIES

The anomalous vessel anastomoses with the other coronary arteries in four different areas. (Fig. 3.)

A. The artery gives rise to descending branches supplying the anterior and lateral third of the left ventricle. Some of these branches anastomose with the branches of the left anterior descending coronary artery. (Area I, Fig. 3.)

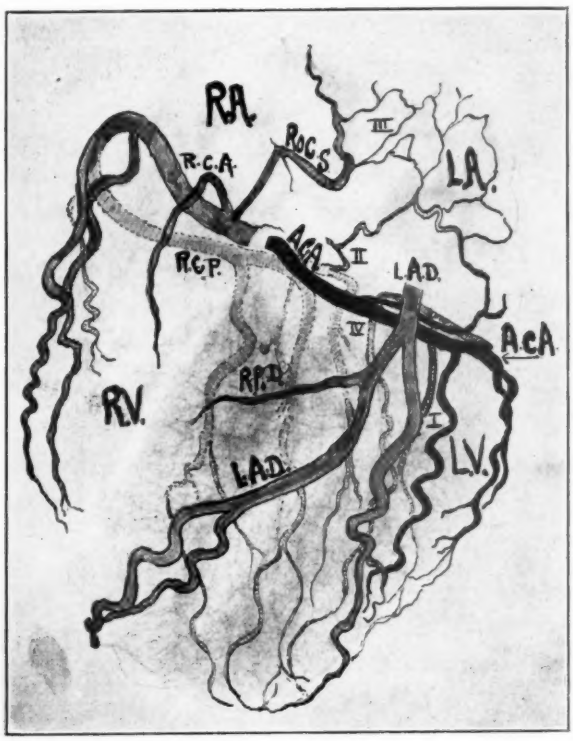

Fig. 3.—Semidiagrammatic sketch of retouched roentgenogram of injected heart (anterior view) showing the origin, course, distribution and areas of anastomoses of the anomalous left circumflex coronary artery. (Shaded black) A.C.A., anomalous left circumflex coronary artery; L.A., left auricle; L.A.D., left anterior descending branch; L.V., left ventricle; R.A., right auricle; R.C.A., right coronary artery; R.C.P. and R.P.D., posterior ventricular branches of the right coronary artery; R.V., right ventricle. Numerals I, II, III, and IV indicate areas of anastomoses.

B. In its course along the auriculoventricular sulcus posteriorly, it also gives off branches which anastomose with the posterior descending branches of the right coronary artery. (Area IV, Fig. 3.)

C. It gives off a branch near its origin which circles to the left and upward in the substance of the left auricle passing over its dome to reach its posterior wall where near the crux of the heart it anastomoses by its smaller branches with the branches of the posterior portion of the right coronary artery. (Area II, Fig. 3.)

D. On its way up the anterior wall of the left auricle the above mentioned branch sends many twigs upward and to the right toward the mouth of the superior vena cava where its ramifications anastomose profusely with the smaller branches of the artery to the sino-auricular node. (Area III, Fig. 3.)

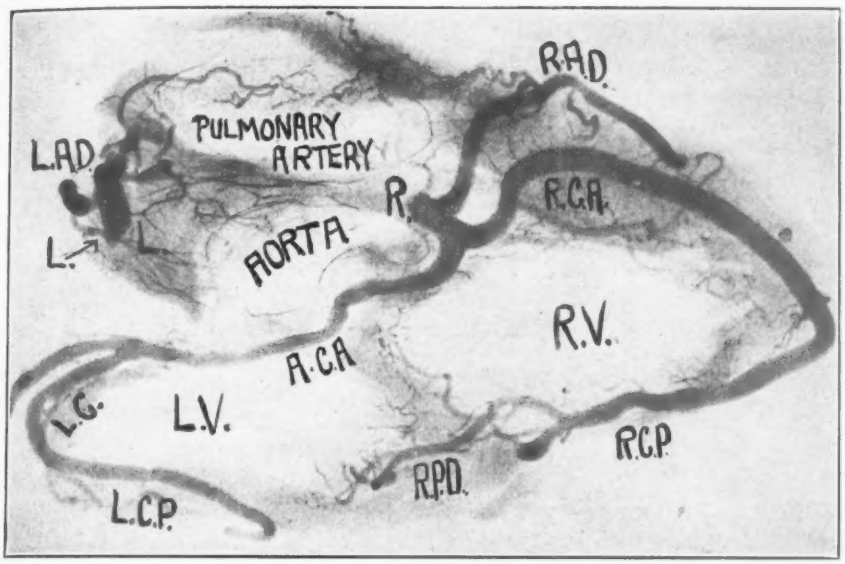

Fig. 4.—Roentgenogram of cross-section of injected heart near the base, showing the origin of the anomalous left circumflex coronary artery (A.C.A.), from the right coronary artery (R.C.A.). L.A.D., left anterior descending branch; L.C.P., posterior ventricular branches of the left circumflex coronary artery; R.C.P. and R.P.D., posterior ventricular branches of the right coronary artery; R.A.D., anterior descending branch of the right coronary artery.

DISCUSSION AND SUMMARY

Four hearts have been studied in which there was an anomalous origin and course of the left circumflex coronary artery. In each heart the left anterior descending branch and the right coronary arteries had their normal origin and distribution. In three hearts the left circumflex coronary artery arose directly from the right sinus of Valsalva, immediately posterior to the origin of the right coronary artery. It then pursued its course posteriorly to the root of the aorta and finally emerged anteriorly between the root of the aorta and the left auricular appendage around the margo obtusus in the auriculoventricular sulcus.

In the fourth case the left circumflex coronary artery arose as a branch of the right coronary artery one centimeter from its ostium. It then maintained a course similar to that described for the left circumflex coronary artery in the other three cases. A point of clinical interest in one of these cases is the fact that the left circumflex coronary artery was normal and patent throughout, whereas the right coronary

artery and the left anterior descending branch presented numerous occlusions (Fig. 2). The clinical history of this fifty-one-year-old man showed ample evidence of repeated attacks of coronary occlusion in the last three years of his life. It seems possible that the independent origin and distribution of the left circumflex coronary artery in this case may have served for a time as a compensating source of nutrition to the myocardium through its anastomoses.

We are indebted to Dr. Louis Gross for the aid he has given in these studies.

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PREMATURE BEATS PRODUCED BY THE MECHANICAL STIMULATION OF THE EXPOSED HUMAN HEART*

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THE observations of Barker, Macleod and Alexander[1] on the exposed human heart, with the analysis of the obtained data, have opened a wide field of controversy relative to the correct terminology to be used in describing premature beats and bundle-branch block. By electrical stimulation of various points on the ventricular musculature they produced premature beats which were recorded simultaneously on the three usual leads. They found in general, that stimulation of the right ventricle produced premature beats with a major deflection of the QRS complex upward in Lead I and downward in Lead III, while stimulation of the left ventricle yielded complexes with a major deflection downward in Lead I and upward in Lead III. These observations were not in accord with the current beliefs which had been largely based on animal experimentation. They suggested that the terminology of premature beats be revised (reversed) to conform to the new findings. They also concluded that electrocardiograms which had been previously thought to represent a block of the left bundle branch, were in reality records of right bundle-branch block and vice versa. Since their original observations, very little evidence has been added to prove or disprove their findings and theories.

Marvin and Oughterson[2] have recorded premature beats produced by electrical stimulation of the heart through a wound made for draining a pyopericardium. The points of stimulation on the right and left ventricles were later checked by post-mortem examination. Their findings confirmed those of the Ann Arbor investigators.

In a pericardiotomy[3] mechanical stimulation of the right ventricle produced premature beats with a major deflection upward in Lead I and downward in Lead III.

In a recent article[4] a case was presented in which an aneurysm of the sinus of Valsalva had nearly completely severed the left main branch of the bundle of His. There was also microscopic evidence of severe disease of the bundle above its bifurcation. The electrocardiogram showed an A-V heart-block and a right bundle-branch block (new terminology). The case was presented as supportive evidence for the original terminology of bundle-branch block. A critical analysis of the record presented, however, seems to show the tracing as that of a complete A-V heart-block with a coincident auricular rate nearly ex-

*From the Morris W. Stroud, Jr., Fellowship in Cardiology of the Pennsylvania Hospital.

actly twice that of the ventricles, rather than a two-to-one A-V heart-block as was the interpretation given.* If this be correct, the case has no bearing on the bundle-branch-block problem, and the conclusions of the author are not justified.

The wide exposure necessary for the removal of an adherent pericardium in a case of Pick's syndrome afforded an excellent opportunity for recording premature beats from known areas of the human heart.

CASE AND METHOD

An American boy, J. W., eleven years of age, was admitted to the Medical Service of Dr. Thomas McCrae for the fourth time in two years, on Nov. 2, 1932. He had been troubled with recurring ascites for nearly four years, which had become so severe in the past few months as to necessitate removal by paracentesis every two or three weeks. There was no past history or family history of rheu-

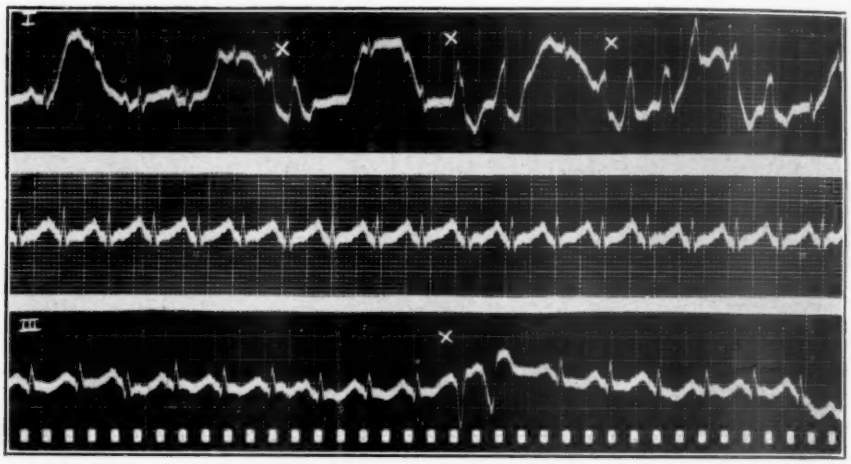

Fig. 1.—Electrocardiogram taken at operation. Leads I and III were taken in succession. Lead II was taken a few minutes later but is added to complete the record. The premature beats shown in Leads I and III were produced by direct mechanical stimulation of the anterior surface of the right ventricle. Time of stimulation marked "X". The main deflection of the QRS complexes of the premature beats is upward in Lead I and downward in Lead III, conforming to the new terminology.

matic fever or tuberculosis. Examination at this time showed an underdeveloped, poorly nourished boy. The venous distention of the neck and arms was striking. The heart was questionably enlarged to physical examination and showed no murmurs. The blood pressure was systolic 90 mm. and diastolic 72 mm. There was no pulmonary congestion or pleural fluid. There was marked ascites with an umbilical and right scrotal hernia. The liver edge was felt 5 cm. below the right costal margin in the midclavicular line and was rounded, smooth and not tender. The spleen was not palpable. Slight pitting edema of the feet and legs was present on admission. The venous pressure was 23 cm. of water (direct and indirect methods), measured at the antecubital fossa.

An x-ray study of the chest showed the heart shadow to be slightly enlarged to the right and left with stereoscopic and fluoroscopic findings suggesting an adherent pericardium.

*This opinion is held by several in addition to the author.

The electrocardiogram on Nov. 3, 1932, showed a normal sinus rhythm with no axis deviation. The P-R interval was 0.18 seconds. The QRS complex showed slurring and very low voltage in all leads. T-waves were iso-electric in Lead I, flattened and diphasic in Lead II and inverted in Lead III.

A diagnosis of Pick's syndrome (concretio pericardii) was made, and as the clinical course was downhill, exploratory operation was advised. On Nov. 11, 1932, Dr. John B. Flick exposed the heart by removing the third, fourth, fifth, sixth and seventh left costal cartilages with a portion of the sternum. The heart was found to be approximately normal in size and its position in the chest was normal. There was an adherent pericardium present with several calcareous plaques, especially in the epicardium of the auricles. During the freeing and removal of the pericardium, it was noted the premature beats were easily elicited by manipulation or touching the heart with any instrument. Electrocardiograms were taken at intervals during the operation and showed premature beats from various foci. At the close a separate record was taken while stimulating a definite area of the heart musculature.

A portable electrocardiograph was used adjacent to the operating table and the time of stimulation noted verbally, the premature beats being observed by the surgeon and on the galvanometer string shadow. Leads I and III were taken in succession. Owing to the long duration of the operation and the condition of the patient, time permitted only the recording of premature beats from one area of the heart. The middle portion of the anterior surface of the right ventricle was chosen because of its accessibility and accuracy of localization. This corresponded to the area of points 6 and 7 in Barker, Macleod and Alexander's case. Several premature beats were recorded in Lead I by touching the heart with a forceps. The irritability of the muscle was such that they were easily produced, two or three premature beats in succession being recorded at times. Only one stimulation of the heart was done on Lead III, two successive premature beats being produced as is shown. The records of Leads I and III taken during the stimulation are presented. Lead II, taken a few minutes later, is included to make the electrocardiogram complete. The undulatory base line in Lead I was present only while the chest was open and is probably of respiratory origin.

CONCLUSIONS

The interpretation of the electrocardiogram published in a recent article is questioned as are the conclusions drawn from the case.[4]

A case is reported in which mechanical stimulation of the anterior surface of the right ventricle of the exposed human heart produced premature beats with a major deflection of the QRS complex upward in Lead I and downward in Lead III.

Further evidence is added in support of the correctness of the new terminology for premature beats and bundle-branch block, suggested by Barker, Macleod and Alexander.

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THE RELATIONSHIP OF ANGINA PECTORIS TO AORTIC VALVULAR DISEASE*

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ANGINA pectoris is not uncommonly associated with disease of the aortic valves. In the majority of such cases, the relationship is a causal one. The specific pathogenesis is usually an obstruction of the coronary ostia by luetic or sclerotic stenosis or by endocarditic vegetations.

Certain cases, however, such as those described by White and Mudd,[1] may show no apparent obstruction of the coronary circulation. These have been explained as being due to the low diastolic pressure of aortic regurgitation, in the presence of which the coronary perfusion pressure is insufficient to maintain an adequate blood supply to the myocardium. Under the circumstances, the occurrence of angina would be favored and in certain instances might depend entirely upon this factor. Recent textbooks[2, 3] have therefore included a low diastolic level among the causes of angina pectoris in cases of aortic insufficiency.

The experimental basis for this view is found principally in the work of investigators who believe that the coronary blood flow is determined largely by the aortic perfusion pressure. Smith, Miller and Graber[4] state that coronary flow depends chiefly upon the height of the diastolic pressure. Anrep and his coworkers[5, 6] found in the heart-lung preparation on dogs, that the mean arterial pressure was the most important value in the maintenance of an adequate coronary circulation. Both groups agree that the myocardial blood flow is significantly diminished by a lowering of the diastolic level as in aortic insufficiency.

Anrep, Davis and Volhard[7] have further maintained that cardiac systole inhibits the coronary blood flow and that the principal flow through the myocardium occurs during diastolic relaxation. An actual backflow of blood during systolic contraction was demonstrated on the isolated perfused heart by Rössler and Pascual.[8] It is therefore concluded that the arterial pressure during systole is not directly effective in the perfusion of the coronary vessels and that the myocardial circulation is diminished by factors such as an increase in pulse rate, which tend to shorten the duration of diastole. If these views be true, it is evident that the low diastolic pressure of aortic regurgitation must be

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an aggravating factor in the incidence of angina pectoris and may, per se, sometimes be sufficient cause for its occurrence.

Hochrein and Keller,[9] however, have recently contested this view. Using more sensitive methods and working on intact dogs with normal respiration and with the coronary vessels unopened, they found that the coronary blood flow is maximal, not in diastole but in systole. In experimental aortic regurgitation, the height of the diastolic pressure was without influence upon the coronary circulation. Support for the validity of these conclusions is found in the work of Keller, Loeser and Rein[10] who have shown that the blood flow through tetanically contracting muscle is increased. It has also been demonstrated by the injection studies of Spalteholz and Hochrein[11] that the myocardial capillaries are not compressed during muscular contraction and that cardiac systole should therefore in no way obstruct the coronary circulation. Finally, Rein[12] has shown on dogs with an intact circulation, that in the presence of a constant venous inflow, the coronary flow increases with an increase in the pulse rate, independently of the height of the aortic blood pressure.

It is beyond the scope of this paper to recapitulate the evidence offered in support of these contending observations, the validity of which must depend upon the accuracy of the methods employed. It was felt, however, that a clinical study of a group of cases with aortic valvular disease might give some indication as to the importance of a low diastolic pressure in the incidence of angina pectoris and from this aspect suggest to what extent the diastolic pressure influences the coronary blood flow. If angina should be found to occur with greater frequency among subjects with low diastolic pressures than among subjects with a similar type of lesion but in whom the blood pressure level in diastole is higher, it may be concluded that aortic regurgitation, per se, is a contributory factor to the production of angina pectoris and that the height of the diastolic pressure significantly influences the coronary blood flow. If no such proportionate relationship appears, however, it would seem that neither angina pectoris nor an insufficiency of the myocardial circulation can be explained on a basis of aortic regurgitation.

METHOD

The present investigation involves an examination of the case records of all patients with aortic valvular disease admitted to the Medical Service of the Krankenhaus St. Jacob, Leipzig, during the past two years. Attention was directed particularly to the incidence of angina pectoris in these subjects and to the height of their diastolic pressure levels.

For the purposes of this study it was essential to include a group of cases covering a wide range of diastolic pressures. In many sub-

jects, therefore, the diastolic level will be found to be well within the normal limits. All patients, however, exhibited definite lesions of the aortic valves. The diagnosis was made on a basis of a characteristic systolic or diastolic murmur at the aortic area, supplemented in the majority of cases by roentgenographic examination and confirmed in those cases on which autopsy was performed. The group was divided etiologically into cases of luetic and nonluetic origin. Only those cases having a positive Wassermann reaction were classified as luetic.* The nonluetic group included patients in whom the aortic valvular disease was due to arteriosclerosis or to endocarditis of rheumatic or bacterial origin.

Great care was necessary in the selection of blood pressure readings which represented an average mean of the variations recorded in individual cases in the course of observation. These variations in some subjects amounted to 30 mm. Hg in the diastolic pressure. In order that blood pressure readings should be comparable, determinations have been used, in the majority of cases, which were made in the Heart Station. These readings were taken under uniform conditions, usually within a few days of admission, with the patient reclining on a couch after a ten-minute rest period. Under the circumstances, patients in whom the diastolic pressure is within normal limits represent cases of aortic valvular disease which tend to have a relatively small amount of regurgitation (the actual index of regurgitation being, of course, dependent upon other factors such as the character of the pulse, the pulse pressure and the rate). They are included in the series for comparison with subjects having a similar pathological condition but a greater degree of aortic insufficiency and lower diastolic pressure levels.

An unquestionable diagnosis of angina pectoris was frequently difficult in a group of patients in whom subjective symptoms are so manifest. Only 16 per cent of the patients in the group were entirely free of cardiac sensations. The remainder complained of varying degrees of palpitation, precordial pain and indefinite sensations of cardiac distress. In many cases, angina pectoris was strikingly simulated. A diagnosis of angina was excluded, however, in all cases in which it could not be made with reasonable certainty. Only those patients were said to have angina who described the pain as having a steady, boring character, located over the upper part of the sternum or in the region of the left nipple. Extension of the pain to the left arm was not constant. It was associated with the characteristic feeling of intense anxiety in approximately one-third of the cases.

*It was recognized that some patients with consistently negative Wassermann reactions may have lues. All questionable cases, however, have been excluded from the luetic group because of the uncertainty of diagnosis and the necessity of satisfactorily explaining the pathogenesis of angina.

RESULTS

Etiology and Age.—Seventy-two patients with aortic valvular disease have been included in the series. Certain facts regarding etiology and age are of interest. Of the total group, 41 cases, or 57 per cent, were due to lues. The incidence of lues is somewhat higher than that reported by other writers[13] probably because of the relatively less common occurrence of rheumatic infection in the locality from which these patients were drawn.[14] Fig. 1 shows graphically the total percentage of subjects in each decade of life compared with the total percentage of subjects in each group in which the etiology was luetic. Before thirty years of age, only 7 per cent of the patients were luetic. With each decade, the incidence of lues increases until in the group over seventy

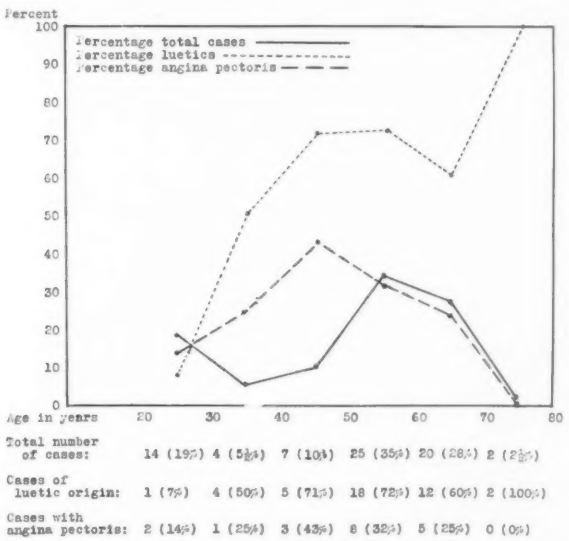

Fig. 1.—Total number of cases, incidence of luetic infection and incidence of angina pectoris in each decade of life.

years, no cases of nonluetic origin are found. This relationship is dependent upon the fact that luetic infection and the development of its cardiovascular manifestations occur at a relatively later period of life than in the case of rheumatic and bacterial types of endocarditis. A further inference from these figures may be drawn as to a relatively better prognosis of longevity in the presence of a luetic etiology. As compared with cases of rheumatic and bacterial endocarditis, this may, however, be more apparent than real, since the duration of life following the onset of valvulitis may be actually longer in nonluetic cases, although the average age of death in cardiovascular syphilis may be considerably later. The fact that no patients in the arteriosclerotic group were over seventy years old may possibly be due to the small number of patients in this group. On the other hand, it might be in-

terpreted as indicating that when the sclerotic process is sufficiently severe to cause such extensive involvement of the aortic valves, a concomitant sclerosis of the coronary vessels leads to a relatively early death. To what extent such factors are responsible can only be surmised. It can be stated with certainty only that in this series of cases, the patients with luetic valvulitis averaged a longer duration of life than did those of nonluetic origin.

Angina Pectoris.—The percentage incidence of angina pectoris is also charted in Fig. 1. This syndrome was present in two of the fourteen patients under thirty years of age. Both cases were of rheumatic origin. Angina is uncommon before middle life, but in young people it is almost always associated with aortic insufficiency.[1] The maximum incidence of angina pectoris in this series occurred in the fourth and fifth decades, thereafter declining rapidly. No cases occurred in the group over seventy years old. Since angina associated with aortic valvular disease usually results from obstruction of the coronary ostia, thus involving an interference with the blood supply to a relatively large area of the myocardium, its appearance, under the circumstances, may be assumed to be a particularly bad prognostic sign.

Congestive Failure.—Angina pectoris usually disappears with the onset of congestive failure. It was important, therefore, for the validity of any conclusions as to the relationship of the incidence of angina to the height of the diastolic pressure to determine to what extent this phenomenon is increased in the presence of low diastolic levels. It was found impractical to estimate the degree of failure for each individual case of this series. The patients were therefore grouped on a basis of whether or not any evidence of congestion was present, simple enlargement of the liver being considered the earliest sign. As might be anticipated, the highest percentage of circulatory failure occurred in the group with the lowest diastolic pressures. Eight patients, or 66.6 per cent, of the group with diastolic pressures below 40 mm. Hg showed evidence of congestion. Between 40 and 79 mm. Hg, 19 patients, or 60.4 per cent, had congestion; while above 80 mm. Hg, congestion was present in 5 patients, or 41.6 per cent. The incidence of this phenomenon is therefore least marked among the subjects with normal diastolic pressures. On the other hand, it is significant that between the group with moderately low diastolic levels and the group in which the pressure in diastole was below 40 mm. Hg, only a negligible difference of approximately 6 per cent in the incidence of circulatory failure was apparent. The level of the diastolic pressure does not therefore seem to be an important cause of circulatory congestion. A factor, evidently of much greater importance, is the degree of the associated damage to the myocardium. The fact that this may be to some extent

proportional to the degree of valvular damage may explain the slight increase in the incidence of congestion in the presence of marked regurgitation.

Subjective Symptoms.—As previously remarked, subjective manifestations are particularly conspicuous in the symptomatology of aortic insufficiency and seem to depend, in part at least, upon the high pulse pressure incident to regurgitation and to the increased velocity of systolic ejection. The physical activity of the patient is unquestionably limited in proportion to the severity of these symptoms. Limitation of physical activity has been suggested as an explanation of the disappearance of angina pectoris with the onset of congestive failure. The same might be said of severe subjective symptoms. The relative incidence of these manifestations has therefore been determined in the present series. Subjects with aortic valvular disease complain usually of severe palpitation and ill-defined sensations of cardiac distress. Precordial pain is often present and differs from the pain of angina pectoris chiefly in its location and in its intermittent, stabbing, rather than steady, boring character. Such manifestations, in varying degrees of severity, were present in 82 per cent of the total group. They occurred in 10 subjects, or 83.4 per cent, of the patients with diastolic levels below 40 mm. Hg, 40 subjects, or 83.4 per cent, of the group with diastolic pressures between 40 and 79 mm. Hg and in 9 subjects, or 75 per cent of the group with diastolic pressures of 80 mm. Hg or above. Thus it is apparent that although palpitation and precordial distress are somewhat less marked among subjects with normal diastolic pressures, the difference is really negligible and does not appear to increase in proportion to a lowering of the arterial pressure in diastole.

Relationship of Angina Pectoris to the Diastolic Pressure.—Of the 72 cases of aortic valvular disease included in this series, 19 subjects, or 26.4 per cent, had angina pectoris. The syndrome varied in type and severity between individuals. In some cases it appeared as a relatively mild angina of effort, in others it occurred in severe spontaneous attacks. In all cases, however, the symptoms were characteristic. Fig. 2 presents the cases divided into three groups according to the height of the diastolic pressure. The total percentage of patients in each group is compared graphically with the percentage of patients in that group having angina. From this it will be seen that of the subjects with diastolic pressures below 40 mm. Hg there were 2 cases, or 16.7 per cent, of the group with a diagnosis of angina pectoris, between 40 and 79 mm. Hg, 16 cases, or 33.3 per cent, and above 80 mm. Hg, one case, or 8.5 per cent. It is evident from these figures that the incidence of angina pectoris does not increase in proportion to a diminution in the diastolic pressure level. Angina is somewhat less frequent in the subjects with the highest diastolic pressures than among those with diastolic levels below 40 mm. Hg. The greatest incidence is found, how-

ever, not at the lowest diastolic levels, as should be the case were low diastolic pressures influential in the production of angina, but in the intermediate group with diastolic levels between 40 and 80 mm. Hg. The presence of a marked degree of aortic regurgitation usually indicates a more extensive pathological condition than is likely to be found in cases in which less significant insufficiency of the valve occurs. It is easy to understand, therefore, why the percentage of angina pectoris is higher among cases in which aortic regurgitation is present (as far as can be judged by the diastolic pressure) than in cases in which the absence of significant regurgitation indicates that the disease process has not been severe enough to disturb the valvular

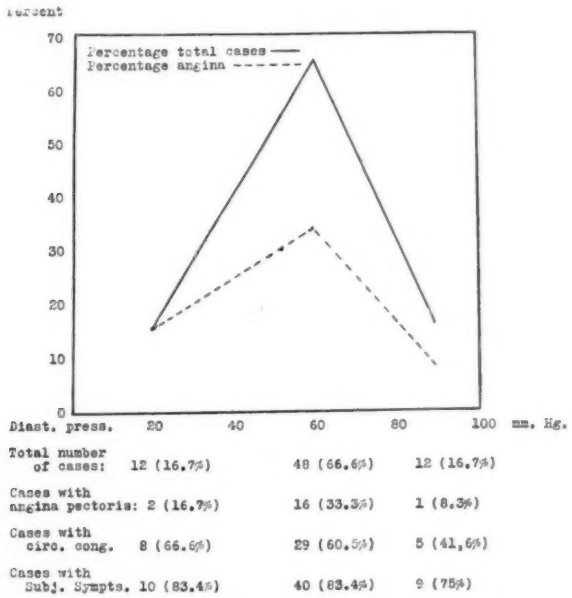

Fig. 2.—Total number of cases and the incidence of angina pectoris, circulatory congestion and cardiac subjective symptoms grouped according to the height of the diastolic pressure.

function. On the other hand, the fact that increasing degrees of insufficiency appear to cause no corresponding increase in the incidence of anginal manifestations indicates that the diastolic pressure level must be of relatively slight importance in determining the extent of the coronary blood flow.

PATHOGENESIS OF ANGINA PECTORIS IN AORTIC VALVULAR DISEASE

The conclusion that angina pectoris cannot be dependent upon a low diastolic pressure receives support if it can be shown that all cases of angina associated with aortic valvular disease can be explained on other pathogenic bases. A vast amount of experimental evidence, which it is unnecessary here to recapitulate, indicates that anginal pain is a

manifestation of myocardial ischemia. On the other hand, the chemical mechanism by which the pain stimulus is produced, the apparent variations in the sensitivity of different subjects to angina, why pain fails to appear in many cases of obvious coronary obstruction and whether vasomotor disturbances of the coronary vessels actually do occur to the extent of producing angina pectoris are points which have not yet been clearly demonstrated. In the present state of our knowledge, therefore, the occurrence of angina is sufficiently explained for the purposes of this investigation if the presence of factors tending to diminish significantly the coronary blood flow, either locally or throughout the myocardium, can be shown.

The pathogenesis of angina in the luetic subjects of this series can be explained in the majority of cases by a stenosis of the coronary ostia which is a usual accompaniment of specific aortitis. Other cases may be explained as being due to loss of elasticity of the aortic wall, as Hochrein[15] has shown that a proportional diminution of the coronary blood flow is associated with this type of pathological condition. Other factors such as coronary sclerosis may, of course, be supplementary. Five of the 19 cases of angina, however, did not have lues and in these the significance of the pain must be otherwise interpreted.

Two of the 5 cases were unquestionably due to coronary sclerosis. Post-mortem examination was performed in one of these and demonstrated widespread calcification of the coronary vessels with complete occlusion of the descending branch of the left coronary artery. The other subject was a male of sixty-seven years showing marked sclerosis of the peripheral vessels. The heart was dilated and there was evidence of adhesive pericarditis. The arterial pressure was 110/70 mm. Hg, so that in any case angina could not be accounted for by a low diastolic pressure.

Two subjects, both males, aged twenty-nine and fifty-eight years, had a history of recurrent attacks of rheumatic fever. Physical examination showed insufficiency of the aortic valves while an apical diastolic murmur indicated that the mitral valves were also involved in the rheumatic process. In both cases, angina pectoris was of the effort type, the pain appearing usually on physical exertion and passing off with rest. Angina pectoris is said to be a relatively unusual complication of mitral stenosis.[16, 17, 18] When this combination does appear, post-mortem examination may fail to reveal any apparent cause for the pain[19] which may be dependent upon a functional stenosis of the coronary ostia.[20]

The fifth subject was a male, aged twenty-seven years. He had a history of recurrent attacks of rheumatic fever, and physical examination indicated an involvement of the aortic and mitral valves. The blood pressure at rest was 150/40 mm. Hg. Attacks of angina were of the spontaneous type. Angina in this case also may have been due

to mitral stenosis. On the other hand, it may be of the type described by Lewis[21] in which angina appears in spontaneous attacks associated with high blood pressure. This syndrome is said to occur frequently in relatively young subjects with free aortic regurgitation. Lewis explained the attacks as being due to a generalized vasomotor disturbance wherein the coronary vessels are so involved that a relative myocardial ischemia is produced. That the attacks are vasomotor in origin is supported by the fact that the pain yields promptly to the administration of nitrites. The patient described above appears very comparable to those discussed by Lewis. He was a tobacconist by occupation and smoked to excess, facts which support the probability of a vasomotor pathogenesis. While no blood pressure readings during the attack are available, the high resting systolic level is suggestive, and the attacks themselves were essentially similar to those of Lewis' subjects.

Thus it appears possible to explain the pathogenesis of all cases of angina pectoris associated with aortic valvular disease without predicating the influence of a low diastolic pressure. Such explanations must be made, however, with the reservation that our understanding of this syndrome is still very incomplete and that forthcoming work may demonstrate the fallacy of many of our present accepted views. But whatever may be the actual cause of anginal pain, it seems very unlikely that a low diastolic pressure plays any conspicuous rôle in its production.

DISCUSSION

The evidence presented as to the relationship of angina pectoris to aortic valvular disease does not appear to be open to serious criticism. In regard to the particular group of subjects studied, in-patients were selected rather than ambulatory cases because in the majority of instances better opportunity had been afforded for thorough investigation and diagnosis. In-patients, furthermore, have had their aortic disease longer as a rule and are therefore more likely to have developed angina than when first seen as out-patients, so that the maximum incidence of angina should be found in such a group.

Factors mitigating the reliability of the figures obtained appear to be chiefly the relatively small number of patients with very low diastolic pressures and the possible influence of congestive failure. A large series of cases is, of course, always preferable. On the other hand, the conclusions would have been as adequately demonstrated if the percentage incidence of angina pectoris had been the same at all diastolic levels while actually it was diminished at low pressures. For this reason it is improbable that chance errors have significantly altered the ultimate conclusions.

That congestive failure or subjective symptoms play little or no part in diminishing the relative incidence of angina is clear from the pre-

ceding observations on these phenomena. The increase in the percentage of patients with low diastolic pressures who showed evidence of circulatory congestion is, in this study, not sufficient to explain the relatively greater decrease in the incidence of angina in the same group. A much more likely interpretation is the probability that if the mean arterial pressure falls to the extent of producing any physiological disturbance, peripheral congestive failure supervenes before the onset of angina. This explanation complements the view that the blood flow through the coronary vessels is modified principally by the work of the heart rather than by variations in the aortic perfusion pressure. Under the circumstances, the coronary circulation would be less affected than would those parts of the circulation which are more dependent upon the arterial pressure. An angina due to insufficiency of the aortic perfusion pressure would therefore not appear until after the occurrence of congestion in the periphery. Congestive failure is not dependent upon valvular competence but rather upon the relative efficiency of the myocardium. Thus even in the presence of a very low diastolic pressure in the aorta, the effective perfusion pressure of the coronary and systemic vessels remains sufficient as long as the myocardium is competent. When the myocardium fails, peripheral congestion appears and angina pectoris does not occur.

The physiological application of these observations lies in the fact that they agree with the conclusions of Hochrein and his coworkers that alterations in coronary blood flow are dependent chiefly upon the work of the heart rather than upon variations in the aortic perfusion pressure and that a low pressure in diastole does not significantly affect the coronary circulation. By the same token, they support the view that cardiac systole does not obstruct the myocardial blood flow. Of clinical importance is their significance in regard to the appearance of angina pectoris in cases of aortic valvular disease. Angina cannot, under the circumstances, be attributed to the low diastolic pressure of valvular insufficiency. Its presence indicates a diminution of the coronary blood flow due to other complicating factors. Of these, aortic valvular disease itself frequently involves blockage of the coronary ostia or loss of elasticity of the aortic wall. Less often is the angina dependent upon purely concomitant factors such as mitral stenosis, vasomotor spasm or coronary sclerosis.

SUMMARY AND CONCLUSIONS

An analysis is made of 72 cases of aortic valvular disease with special reference to the relationship between the incidence of angina pectoris and the height of the diastolic pressures. Etiology and age are discussed.

Angina pectoris occurred in 8.3 per cent of the cases in which the diastolic pressure was 80 mm. Hg or above, 33.3 per cent of the cases

in which it was between 79 and 40 mm. Hg, and in 16.7 per cent of the cases in which it was below 40 mm. Hg. The fact that this syndrome did not occur most frequently in the latter group indicates that a low diastolic pressure is of relatively slight importance in the pathogenesis of angina pectoris. The incidence of congestive failure was also studied, but its increase at low diastolic levels was insufficient to account for the relatively greater decrease in the incidence of angina in the same group.

These observations indicate that the appearance of angina pectoris in cases of aortic regurgitation cannot be attributed to an insufficiency of the coronary perfusion pressure during diastole. They support the view of Hochrein that the work of the heart is the most important factor in determining the volume of the coronary blood flow, that the myocardial circulation is relatively little affected by alterations in the diastolic pressure level and that cardiac systole does not significantly obstruct the coronary vessels.

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THE PROGNOSIS IN GONOCOCCAL ENDOCARDITIS*

Review of Literature and Report of Case with Spontaneous Recovery

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THE writings of Ricord[1] in his classical treatise on venereal disease were probably the first demonstration of the fact that gonorrheal infection may go to systemic distribution with visceral involvement. It is this work that indicated clearly that gonococcus infection may involve the heart. The first clinical demonstration of gonococcal heart disease was that of Brandes,[2] whose paper seemed to demonstrate clearly that there was a connection between the onset with an acute urethritis and the cardiac involvement. If the clinical observations of Brandes are indubitable, his is probably the first recorded case of gonococcal endocarditis with recovery. At this point, it may be said, that early writers recognized that gonococcal endocarditis may follow urethritis without the appearance of arthritis.[3-8] Lucas[9] found arthritis absent in fifteen cases out of forty-three. The first recorded recovery of the gonococcus from the circulating blood was probably that of Rothmund,[10] and elaborated on more fully by Souplet.[11] Hewes[12] soon followed thereafter with reports of positive blood cultures in gonorrheal polyarthritis. The first demonstration of gonococci in the valves in cases of gonococcal endocarditis was that of Rendu and Halle.[13] In the German literature, an early report concerning gonococcal endocarditis was by Shedler,[14] which is of particular interest because it treated of a fatal case with complete post-mortem findings. Desnos[15] demonstrated specimens with endocarditic involvement as early as 1877. These specimens were from a man who developed arthritis as a sequel to a urethritis, and in the midst of a severe febrile course an endocarditis was found to be present. Polypoid vegetations of a characteristic variety were found on the mitral and aortic cusps. In Shedler's case, the presence of nephritis was emphasized; of unusual interest in the light of the fact that clinical studies of gonococcal endocarditis in recent years (Thayer, etc.) have revealed not a few cases with renal involvement, some with actual termination in uremia. The report of Delprat[16] included two cases, one with recovery; this case having developed loud cardiac murmurs a few days after the cessation of a thick urethral discharge, the patient having been discharged with severe endocardial involvement. Morel[17] described a case in which healing took place; in this instance

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on the third day of a febrile period, the hitherto rich urethral discharge diminished, at which time a loud apical systolic murmur was found to be present for the first time. Subsequently there set in an arthritis of the left knee joint and fourteen days after, amid chills and fever, a diastolic murmur appeared at the base of the heart with the coincidental appearance of severe dyspnea. The patient died six weeks after the onset. An early instance where the organisms were found post mortem on section but not ante mortem in the circulating blood is recorded by Wilms.[18] It was this author's belief that the organisms found in the valves were pyogenic bacteria which entered the circulation after involving the urethra as secondary invaders. The organisms found on the heart valves were described as intracellular diplococci for which reason the theory of secondary pyogenic invasion is doubtful. The report of Loeb[19] is interesting because it considers the pleuropulmonary complications among the other visceral manifestations of gonorrhea; a subject which in recent years has been reconsidered by Pratsicas.[20] The latter writer describes a case with systemic infection in which a pleural effusion developed from which organisms were recovered having the morphological characteristics of gonococci. This patient had no endocardial involvement clinically demonstrable. The offending organisms could not be identified culturally because they failed to survive on subculture. Bressel[21] described a case of gonococcal bronchopneumonia in which the gonococci were recovered in the sputum. Similar reports were made by Wynn,[22] Scherrer,[23] Barbiani[24] and Ahman.[25]

Lenhartz[26] in his classical work expressed the opinion that recoveries in gonococcal endocarditis sometimes do occur. He quotes the case of a sixteen-year-old girl who eight weeks before coming under his observation had had an acute gonorrhea. Four days before admission dyspnea, precordial oppression and severe constitutional symptoms set in. The urethritis and endocervicitis were severe, and smears taken locally were positive for gonococci. Unusually loud systolic and diastolic murmurs were heard at the base which subsequently completely and permanently disappeared. During the acute febrile course there were two chills, high intermittent fever and practically no local evidence of disease. Blood cultures were not reported. The absence of local disease (urethritis, etc.) is a fact that has been particularly emphasized also in recent years. Lenhartz judiciously laid stress on the difficulty of interpreting clinical findings because he felt certain that systemic gonococcal infection could readily occur in people with old rheumatic valvular disease; for which reason he cautioned against the indiscriminate assignment of a gonococcal etiology in these cases. Karsner[27] recently made the statement that in order to establish the diagnosis of gonococcal endocarditis the presence of gonococci in the blood or the lesions must be shown. This attitude contrasts sharply with that of Jagie and Schiffner,[28] who within fairly recent years expressed the

opinion that mild cases of gonococcal sepsis occur with endocardial involvement which not infrequently go on to complete recovery. These writers believe that if there is no other etiological factor for cardiac disease and cardiac involvement occurs in the course of a full-blown gonococcal infection, the diagnosis of gonorrheal heart disease is warranted. They feel that in the verrucose form of gonococcal endocarditis as contrasted with the ulcerative form, cases frequently go on to a termination with complete recovery, but in most cases a valvular defect remains. They also are of the opinion that the verrucose form of endocarditis is not so infrequent as the ulcerative form. They cite the case of a thirty-eight-year-old male who following an acute urethritis developed a complicating epididymitis. Three weeks thereafter during an acute febrile period a blowing systolic murmur was heard at the apex, and in yet another three weeks the left ventricular border was found to be displaced to the left. The systolic murmur increased in intensity. On discharge, the heart showed outspoken cardiac enlargement with a heaving apical impulse, a loud systolic murmur at the apex and an accentuation of the second pulmonic sound.

Concerning the general subject of gonococcal endocarditis, the literature abounds in descriptions of the clinical course, bacteriological and pathological findings in this disease. In the last decade and a half, over one hundred reports have appeared on the subject. The German literature emphasizes particularly the pathological aspects of the disease; the French, the bacteriological; the American, the clinico-pathological. Of the almost innumerable reports of fatal cases, there may be mentioned those of Vander Veer,[29] Lefebure,[30] Edwards,[31] McCants,[32] Lion and Levy-Bruhl,[33] Dwyer,[34] Riecker,[35] Johnston and Johnston,[36] Gill,[37] Klein,[38] Warfield,[39] Bard, Langernon and Gardere,[40] Gallavardin,[41] Lartigan,[42] Villela and Torres,[43] Smith,[44] Galois,[45] Barbe and Meynet,[46] Brebner,[47] Kramer and Smith[48]; and more recently there have appeared the reports of Kirkland,[49] Cooper and Klinck,[50] and Hoffman and Taggart.[51] The attitude of these writers concerning the prognosis in gonococcal endocarditis varies widely. Thayer,[52] whose monograph on this subject will remain one of the classic reviews of the disease, is of the opinion that recoveries do occur in gonococcal endocarditis, but are probably extremely rare. Warfield in his report expresses the belief that no true cases of gonococcal endocarditis recover. Libman[53] makes the statement that while all cases of acute bacterial endocarditis are said to be fatal without exception, the impression he had gained was that acute gonococcal endocarditis seemed to carry the best prognosis.

A survey of the early literature on the subject of recoveries in cases of gonococcal endocarditis, reveals that the first recorded case is that of Brandes, as has already been mentioned. The writings of the pre-bacteriological days are from time to time involved in the reports of

such cases; viz., Delprat,[16] and Morel.[17] The report of Lenhartz[26] cited previously represented clearly a recovered case. The only source of possible doubt was the failure to recover the gonococci from the circulating blood. The clinical course was typical from every point of view except for the fact that no embolic lesions appeared at any time. Gourvich[54] in his report of a recovered case reviewed the cases of recovery to that time. He failed, however, to distinguish between hemic murmurs that arise in the course of an acute febrile disease and the organic murmurs of true gonococcal endocarditis. Thayer[52] in this connection remarks very properly that early endocarditis is often difficult to recognize, as is the case in rheumatic fever, and just what relationship there is between murmurs heard during an acute gonococcal infection and preceding chronic valvular disease is often impossible to say. Unger[55] cited a case of an eighteen-year-old boy who developed a fresh endocarditis with an apical systolic murmur and functional insufficiency. He ran an irregular fever, developed arthritis and eventually recovered. Blood culture during the acute phase of his illness was positive. The classic case of Silvistrini[56] is worthy of review in detail. This case probably represents the first record of systemic gonococcal infection with blood stream invasion, polyarthritis, endocarditis and jaundice. The patient was a male of twenty-nine years, who one month before his admission had contracted a gonococcal urethritis. Twenty days after the cessation of the urethral discharge, he was taken with malaise, chills and fever. Three days later an acute polyarthritis set in involving the wrists and metacarpophalangeal joints. Seven days after the onset of the fever, icterus of the skin and mucous membranes appeared. The urine showed the presence of bile but no albumin or sugar. On the thorax there appeared several erythematous hemorrhagic blebs. The liver and spleen were enlarged. A systolic murmur was heard at the apex of the heart, transmitted to the axilla. Subsequently, involvement of the ankles, wrists and knees set in. Upon the day after admission, a pericardial rub was heard; jaundice became deeper, the liver larger. After an illness of three months' duration the patient recovered and was discharged with ankylosis and stiffness of the joints and a full-blown mitral insufficiency. Blood cultures done on enriched media, viz., glucose serum and pleural fluid, grew out the gonococci. Smears of a milky fluid obtained from one of the involved joints showed leucocytes within which were numerous gram negative diplococci. An opinion as to whether this represents a truly recovered case of gonococcal endocarditis must be held in abeyance; the failure to report changes in character of the cardiac lesions makes one suspect that the writer was more probably dealing with a case of gonococcal sepsis with icterus than with one of true gonococcal endocarditis. Withington[57] cited the case of a thirty-six-year-old male with a urethritis of one and a half months' duration who developed an acute aortic

endocarditis which was found to be present on admission. He ran a febrile course with chills and fever, but no arthritis was present. Blood cultures revealed the presence of gonococci. This patient went on to complete recovery with no signs other than the persistence of a systolic murmur at the base of the heart in the second left interspace. During the acute febrile period, precordial pain, orthopnea, cardiac enlargement, pericardial friction rub and gallop rhythm had been present. Dieulafoy[58] described a case of recovered gonococcal endocarditis in which the differential diagnosis from typhoid fever became a problem. The patient was a male of twenty-three years whose illness had an acute onset with high remittent fever. Urethritis was present one month before admission. Sweating, headache and diarrhea were present after the onset. Because of the profuse diaphoresis, the diagnosis of typhoid fever was questioned. There was no arthralgia present at any time. Two days after the patient was first seen, a mitral murmur was heard of a scraping musical quality, for which reason it was supposed that an ulcerating endocarditis was present. Hemorrhagic papular skin lesions occurred on the abdomen, thorax and thighs. There was a severe secondary anemia associated with a leucocytosis and polyneucleosis. The urethral smears showed the presence of gonococci. The blood culture likewise was positive for gonococci. The patient was treated with gonococcus vaccine, and despite the occurrence of a complicating bronchopneumonia, recovery took place in forty days after onset. The patient was left with a permanent mitral lesion. Faure-Beaulieu[59] reviewed thirty-four cases of gonococcal sepsis in an excellent monograph on this subject. Of these patients, ten died. Of the twenty-four recovered cases, in three, apparently definite endocardial involvement was present. Undoubtedly prompted by the reported success of vaccine therapy in this disease, as well as with the use of anti-gonococcal serum, Schiele and Dorbeck[60] used an antiserum in a case of severe gonococcal sepsis in which an acute endocarditis was said to have been present. In one month the fever subsided in their case and the cardiac signs disappeared. Sagot[61] quotes the case of Marfan and Debric as illustrating the occurrence of gonococcal endocarditis with recovery. A ten-year-old girl was seen with a week's history of abdominal pain and gave a typical typhoidal appearance. There was marked abdominal distention, but no vomiting or diarrhea. The diagnosis of pelvic peritonitis was made. A vaginal discharge revealed, however, the presence of gonococci. The heart was found to be slightly enlarged to the left in the fifth interspace just outside the nipple line. There was also slight cardiac enlargement to the right. A systolic thrill was present at the apex as was an intense rough systolic murmur which was transmitted to the axilla. A mitral endocarditis was thought to be present, and in view of an entirely negative past history, the cardiac lesion was presumed to be a recent one. Two days after admission

a mesodiastolic murmur was heard. The blood culture revealed the presence of the gonococcus. The patient was given in addition to local therapy for the vaginitis, gonococcus vaccine. She recovered three weeks later, with signs of a mitral valvulitis and adherent pericardium. These signs were found to be present on examination ten months after the onset. Luithlen[62] reported a case of a twenty-six-year-old male taken with acute posterior gonococcal urethritis. One month afterward, during which time the urethritis was being treated, he complained of cardiac pain. Cardiac findings at this time were a soft systolic murmur at the apex, slight cardiac enlargement to the left and a bradycardia. The next day the patient went into cardiac collapse; he then became slightly febrile and the spleen became just palpable. Temperature became normal five days after this episode. He eventually recovered. The author of this report feels that this represents a case of recovered gonococcal endocarditis. More recently, Aubertin and Gambillard,[63] citing the successful use of anti-gonococcus serum at the hands of Schiele and Dorbeck, previously quoted, undertook the use of this form of therapy in the treatment of a case of gonococcal endocarditis that came under their care. An eighteen-year-old male came under their observation following the onset of an illness ushered in with a shaking chill. The less immediate illness dated back to the onset with an acute urethritis which the patient treated with self-medication. Nine months later, arthralgias, unassociated with fever set in, for which five injections of gonococcus vaccine were given. At the time marked pallor of the skin and mucous membranes was noted. Two months thereafter, a systolic murmur was discerned at the base of the heart, and a leucocytosis and polyneucleosis were found to be present. Two days after the systolic murmur was discovered, a diastolic murmur at the base of the heart was heard. At no time was there a Corrigan pulse present. The spleen was not palpable; the urine was negative. After one month of a severe febrile course, anti-gonococcal serum was administered, in all eight injections of 40 c.c. were given. This was followed in due time by a severe serum sickness, characterized by arthralgias and urticaria, following which the patient became afebrile. During the course of this severe febrile illness, six blood cultures were taken, all of which showed no growth. It is obvious from a review of this case, that the writers were not dealing with a case in which endocarditis was definitely present. The time of onset with systemic symptoms post dates the onset with acute urethritis by a period of time which exceeds by many months the usual period when endocarditic involvement takes place. The absence of embolic phenomena, palpable spleen and positive blood culture tends to support the view that an actual gonococcal endocarditis was not present in this case. Schottmüller[64] in his treatise on sepsis expresses the feeling that one

must be cautious before giving an absolutely hopeless prognosis in gonococcal endocarditis. He cites recovery in a case he himself saw in addition to a case reported by Jochmann. Leschke[65] reported a recovered case in which we find that the critical drop in temperature occurred following a febrile episode during which the temperature was the highest that it had been at any time during the illness. In the case that I shall quote as a recovered case of gonococcal endocarditis, the same phenomenon occurred. Some writers invoke the theory of extreme thermolability of the gonococcus as a cause of self-sterilization, so to speak. It is, to be sure, a subject of much speculation, and one with which I shall not attempt to cope. Prendergast[66] remarks on the general character of gonococcal endocarditis by saying that it does not differ essentially from other forms of acute bacterial endocarditis, except that the outlook for life is better. Of two cases known to that writer, one recovered. He feels also that if an acute endocarditis occurs in a patient with gonorrhea and no organisms can be recovered, because of the well-known difficulty in culturing the gonococcus, the presumption is that a gonococcal endocarditis is present. The recovered case he cites is that of a man of twenty-four years whose illness began with a urethral discharge, followed in one month with epididymitis. About six weeks later he complained of pains in the extremities and precordia, at which time the heart was normal in size and no murmurs were heard. Two days later there was increasing fever, sweating and prostration. The heart was enlarged, and long soft mitral systolic and short aortic diastolic murmurs were heard, followed in two days by a pericardial rub. Sixteen days after onset of precordial pain a pericardial effusion was present, and in one month the effusion was gone. The patient approached normal but the murmurs remained. He was seen five months later and a faint aortic diastolic murmur was heard, there was a large pulse pressure present, but he was otherwise normal.

Within the last two years there have appeared two reports of unusual interest in connection with the surgical therapy of gonococcal bacteremia in women, by the radical extirpation of diseased foci in the pelvis. The earlier report of Wheeler and Cornell[67] concerns the recovery of a nineteen-year-old female who had an intermittent bacteremia of pelvic origin, from whose blood stream the gonococci disappeared following radical extirpation of the diseased foci in the pelvis. Gonococcal endocarditis was not definitely established in this case. Encouraged by this result and feeling that gonococcal endocarditis carried with it such a bad prognosis, Garlock[68] described a similar case with a successful surgical result. A female of twenty-six years came under his observation with fever and a rash of four weeks' duration. The onset was with a chill which had recurred one week thereafter. Pain and stiffness in the ankles set in; there was no previous history

of rheumatic fever or chorea, nor of gonorrheal infection. The heart was found to be slightly enlarged to the left, and a soft systolic murmur was heard at the apex and a rough systolic murmur at the pulmonic area. The spleen was not felt. The skin of the back and of the front of the chest was covered by a macular rash. Pelvic examination showed only a boggy uterus. The urine was negative; there was no anemia; a leucocytosis was present. The blood cultures grew out the gonococcus on three occasions, and the cervical smears also showed the presence of the gonococcus. The heart became enlarged under observation, and systolic and diastolic murmurs were heard at the apex. Anemia then ensued. The diagnosis of gonococcal endocarditis was made, and since it was felt that the prognosis was hopeless, salpingohysterectomy was performed. The patient's temperature promptly fell to normal, and she was discharged after seven weeks, all blood cultures during this time being sterile. The patient was seen six months later, and no pathological changes could be discovered in the heart. This patient had also had the benefit of five transfusions during the course of her treatment. The value of repeated transfusion in the treatment of gonococcal endocarditis is the subject of a paper, by Perry,[69] dealing with a recovered case. A male of twenty-two years first came under his observation with a complaint of fever of one week's duration. The patient had had a urethral discharge for the three months previous to the onset of the acute illness. He had been through an insurance examination the year before, and no cardiac murmurs were noted. One week after he was first seen he had a chill and a rise of temperature to 105°. The heart revealed in addition to a tachycardia, a slight enlargement to the left. At the pulmonic area a soft low-pitched murmur was heard, systolic in time. A few days later a diastolic murmur appeared at the pulmonic area. Blood culture grew out the gonococcus. The patient was given repeated small transfusions, went through several episodes of pulmonary embolism, recovered and was discharged well after four months. In all, fourteen transfusions were given, and one injection of convalescent serum was given. The patient was seen one and a half years later. The author of the report informs me[70] that the patient is clinically well and has a definite pulmonary insufficiency which is causing him no symptoms. In this connection it is interesting to note that in the paper of Libman previously cited[53] a case of gonococcal endocarditis involving the pulmonary valve which went on to spontaneous recovery seen by Doctor Edward Janeway, was mentioned.

At the Mount Sinai Hospital, New York City, up to the present date there have been seven cases of gonococcal endocarditis. In all of these except the case described there was a fatal issue. Because of the rarity of recovery in this disease and the remarkable clinical course, the following case is reported:

REPORT OF CASE

E. S. Acc. No. 334293, Aged nineteen years, an unmarried stenographer, entered on the First Medical Service of Doctor Leo Kessel, The Mount Sinai Hospital, on January 15, 1932. She was discharged well on February 27, 1932. She was an American born girl who with the exception of a five months' stay in Florida, during 1930, had always lived in New York City. She denied ever having had pneumonia, typhoid fever, scarlet fever, diphtheria, chorea, frequent sore throats, "heart trouble," or rheumatic fever. At the age of ten years, a tonsillectomy had been performed. Her menses commenced at twelve years, were always regular and lasted four days. Her last menstrual period had occurred in December, 1931. She had missed three periods during her pregnancy (see present illness). Her present illness began three months before admission, when, in an attempt to terminate a pregnancy of four months' duration which was associated with morning nausea and amenorrhea, she went to a midwife who inserted a heavy gauze pad into the vagina. This, the patient removed twenty-four hours later with a small blood clot. This was accompanied by severe lower abdominal pain of a cramplike character, followed twenty-four hours later by a steady severe knifelike pain in the right lower quadrant which was increased by coughing and breathing, and unaffected by urination or defecation, which two functions were normal. There was no nausea or vomiting. The temperature rose to 104° and returned to normal the following day. She was up and about for one week when the lower abdominal pain returned this time more severe on the left side. At this time the patient had a curettage of the uterus performed. Pain remained persistent for the two months thereafter and was accompanied by daily rises of temperature to 105°, associated with profuse sweats. There had been no vaginal discharge except for a foul bloody one, one week after the clot was passed at the onset. There was no epistaxis, no respiratory symptoms, no tender finger tips or toes. Six days before admission she had received a 500 c.c. transfusion. Physical examination on admission revealed a chronically ill, underdeveloped female with marked pallor of the skin and mucous membranes. The skin of the entire body was slightly of a café-au-lait hue. No petechial spots were seen anywhere on the skin or mucous membranes and no splinter hemorrhages under the finger nails. The pupils were round, regular and reacted to light and accommodation. The sclerae were not icteric. The fundi were normal. The teeth were in poor condition, and the tongue was coated; there was slight fetor oris. The pharynx was slightly red; the tonsils were cryptic. There was no lymphadenopathy. The lungs were negative. The heart was not enlarged to the right or to the left. There was no increase of cardiac dullness over the pulmonary conus. The apex impulse was forceful. There were no murmurs heard. A_2 was greater than P_2. The rhythm was regular. The spleen was felt two and a half fingers below the subcostal margin; the edge was firm. No perisplenic friction rub was heard. The liver edge was felt one finger breadth below the right subcostal margin. On pelvic examination, the cervix was found to be slightly patulous and eroded. A slight mucoid discharge issued from the os uteri; the findings were otherwise negative.

Laboratory Data: Hemoglobin 62 per cent, R.B.C. 4,550,000; W.B.C. 5,400, Polys. 83 per cent, of which 9 per cent were staff cells. There was marked toxic granulation of the polynuclears. Platelets 250,000. B.P. 108/70 mm. Wassermann and Kahn tests, negative. Blood urea nitrogen 11 mg. Sedimentation time forty minutes. Tourniquet test negative. Cervical smear for gonococci negative. Urine on admission was acid in reaction, contained one plus albumin, no sugar, and 2-5 R.B.C. per high power field, and numerous W.B.C., hyaline and granular casts were seen microscopically. Urine concentration test 1.006 – 1.014.

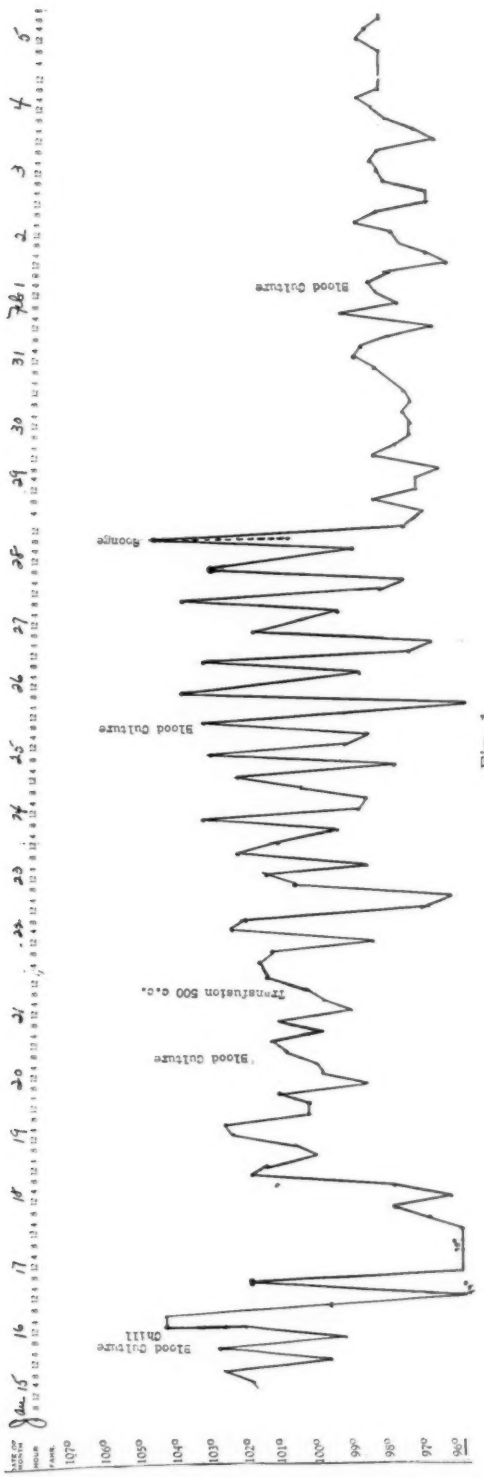
Blood Culture
Chill
Blood Culture
Transfusion 500 c.c.
Blood Culture
Sponge
Blood Culture

Fig. 1.

Clinical Course: The temperature the day of admission was 104.4°, following a short shaking chill. Blood culture taken after the chill revealed the presence of gonococci in all the fluid media. This finding was confirmed on three occasions. The gonococcus-complement fixation was four plus. Two days after admission, a soft diastolic murmur was heard over the sternum at the level of the third interspace. Three days later a white centered petechia was seen in the right lower conjunctiva. At the same time, a small red lesion, which was tender, appeared on the dorsum of the left foot—a metastatic focus. This lesion disappeared in two days. The anemia progressed, the hemoglobin dropped to 53 per cent. For the first week there was no recurrence of the chills. One week after admission a 500 c.c. transfusion was given, as a result of which the hemoglobin rose to 62 per cent. Eight days after admission, fluoroscopy of the chest was performed which revealed that the left ventricle was enlarged downward and to the left, and that there was some prominence in the region of the left auricle in the posterior anterior position, but no evidence of enlargement was seen in the right oblique position, the aorta was dilated, its excursions wide. The appearance was that of an aortic insufficiency probably associated with a mitral lesion. The blood pressure dropped from 108/70 to 90/30 mm. The endocardial murmur was observed to become more pronounced during the patient's stay. Profuse sweats occurred. The temperature ran a septic course (see chart, Fig. 1) for two weeks. On the fourteenth day after admission, January 28, 1932, the temperature rose to 104.8° at eight o'clock in the evening, to fall to 97.8° at midnight. It thereafter never rose to a point above 99.6°. Six weeks after admission, or four weeks after the defervescence of the fever, the spleen was found to have receded to a point one finger breadth below the left subcostal margin. The blood pressure on discharge was 120/58 mm. One week after the remission of the fever, the urine showed no albumin, no formed elements and was guaiac negative. Electrocardiogram revealed no definite abnormality. Blood culture taken on the fifth day after the remission of the fever was sterile.

Follow-Up Reports: March 28, 1932, blood pressure 110/30 mm. Patient felt entirely well. No dyspnea or swelling of the ankles. No Corrigan pulse present. No urinary complaints. Spleen palpable one and a half fingers below subcostal margin. May 23, 1932, patient felt entirely well, had had no dyspnea. No swelling of the ankles. No congestive signs in the lungs. A soft diastolic murmur was heard at the second left interspace transmitted along the left border of the sterum. Spleen felt one and a half fingers below subcostal margin. Heart slightly enlarged to left on percussion. Blood pressure 110/48 mm. June 27, 1932, patient felt well, had no complaints referable to cardiac or any other system. Examination of the heart revealed very short systolic murmur to second right interspace and an impure second sound to left of sternum in third interspace. July 25, 1932, patient felt perfectly well. There was no dyspnea or pulmonary congestion. Soft diastolic murmur was heard along the left sternal border. First heart sound loud. P_2 louder than A_2. Blood pressure 140/60 mm. Spleen felt one finger below costal margin. July 26, 1932, Hemoglobin 90 per cent. October 24, 1932, patient perfectly well. Blood pressure 124/68 mm. Apical systolic murmur with accentuation of P_2 and very low-pitched diastolic murmur heard next to the sternum.

COMMENT

We were here dealing with a case of gonococcal endocarditis which developed in the course of a gonococcal bacteremia, following an induced abortion by tamponage and subsequently by curettage. This sepsis had run a chronic course of three and one-half months' duration preceding admission to the hospital. No valvular lesion was present

on admission nor was there anything in the past history of the patient, by direct questioning or by symptomatology to suggest antecedent valvular disease. During her course in the hospital which was markedly septic, an aortic and mitral insufficiency developed, confirmed by fluoroscopic examination and by an increase of pulse pressure under observation. The septic course went into spontaneous remission four months after onset; the patient having developed peripheral embolic phenomena, a focal glomerulonephritis, then went on to recovery and was discharged with an aortic and mitral insufficiency.

SUMMARY

Gonococcal endocarditis does not necessarily carry with it a fatal prognosis. The literature on reported cases of recovery in gonococcal endocarditis is reviewed in detail. A case of postabortal gonococcal sepsis with gonococcal endocarditis, with peripheral embolic phenomena, focal glomerulonephritis and valvular insufficiency which developed under observation and which underwent spontaneous recovery, is reported.

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RUPTURE OF THE AORTA*

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IN AN extensive review of eighty-three cases of rupture of the aorta with dissecting aneurysm, reported prior to the year 1863, Peacock[1] states that Mannoir first described the condition in 1802; however, the lesion was not generally appreciated until Laennec's work in 1826. A more recent survey made by Resnik and Keefer[2] shows a total of 200 reported cases. Much space has been given to the discussion of this condition by a number of competent men who have repeatedly covered the clinical and gross pathological aspects.

A classification of ruptured aortas based entirely on etiology is not possible with our present knowledge of the subject. Whitman and Stein,[3] Shennan and Pirie,[4] Resnik and Keefer,[2] Klotz and Simpson,[5] and others, have suggested classifications. Most cases tend to fall into definite group which may be listed as caused by: (a) trauma, (b) extrinsic erosion, (c) hypoplasia, (d) coarctation, (e) inflammation, and (f) degeneration.

The confinement of fluid in any given space depends upon two factors, viz., the strength of the container and the pressure exerted upon it by the confined fluid. Both factors may be altered simultaneously in the human aorta; therefore, more than one important change may be present in any given case of rupture. Furthermore we must conclude, whether it can be demonstrated or not, that there has been an alteration of at least one of these forces. Klotz and Simpson[5] found in testing aortas of individuals between the ages of twenty and forty years that a pressure of 1000 mm. of mercury was not sufficient to rupture its walls. Oppenheim[13] found that rupture occurred at about a pressure of 3000 mm. of mercury in normal human aortas. Moritz[14] found that pressures of from 800 to 1200 mm. of mercury induced through a cannula inserted in the proximal end of the aorta of living rabbits resulted in rupture of the portal vein or its tributaries. The aorta could not be ruptured because of the rapid flow of blood through its peripheral circulation. Sudden changes of pressure will have a much greater effect than a continuous force; consequently these figures are higher than those in the sudden tearing force necessary to burst the vessel. Cases of rupture of the aorta associated with chronic high blood pressure are relatively frequent (Lifvendahl,[15] Oppenheim,[16] Busse,[10] Loffler,[17] Strickland,[18] McLean and Fiddes,[19] and many

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others). Unquestionably altered blood pressure plays a very important rôle in rupture of the aorta; it must be of the greatest importance in cases associated with coarctation. From the above experimental data it is difficult to conceive of any blood pressure ordinarily present being sufficient to burst a normal aorta.

Trauma.—Terrific blows to the thoracic cage have repeatedly resulted in the rupture of aortas which have been considered structurally normal (Rolleston,[6] Kemp,[7] Griffiths,[8] Jaffe and Sternberg,[9] and Busse[10]). Flying objects such as blocks of wood or stone, train and automobile accidents, falls from high buildings, bridges and aeroplanes, have all been found the cause of bursting of the aorta. This result is apparently due to the sudden transmission of the force of the blow to the confined noncompressible blood. It is interesting that in traumatic ruptures, as in rupture due to other causes, the site of predilection is in the ascending portion of the arch and at the duct of Botalli, thus favoring either Rindfleisch's[11] theory that these areas being comparatively fixed are predisposed to injury, or Abbott's[12] belief that the aorta may be congenitally weak in these regions. Rupture of the aorta from any cause results in the formation of dissecting aneurysm in a majority of cases. This phenomenon of dissection of the aortic wall, we feel, is the result of the right angle deflection of the rupturing force due to the greater elasticity of the adventitia in the traumatic cases, and to degenerative changes in the media in addition to the elasticity of the adventitia in the nontraumatic cases.

Extrinsic Erosion.—The compact walls of large blood vessels are relatively immune to the penetration of bacteria and malignant tumor processes extending from surrounding organs. Rupture due to erosion of the aortic wall by such lesions as mediastinal tuberculosis, carcinoma of the esophagus and similar lesions of the lungs and vertebrae is not uncommon and because of its general recognition will not be discussed further.

Hypoplasia.—The rupture of hypoplastic aortas, a condition generally associated with status thymolymphaticus, has been described by Richey,[20] George,[21] Marine,[22] and others. These congenitally small thin aortas show a diminution in the breadth of all three layers of the wall but especially of the media, otherwise the structure is not markedly altered. This weak vessel may not withstand even the normal variations of aortic pressure.

Coarctation.—Of the 200 cases of coarctation of the aorta summarized by Maude Abbott,[12] 38 patients died of spontaneous rupture of the aorta. In Oppenheim's[23] case the wall was apparently healthy and rupture was thought to be due to the effect of a sudden increase in pressure acting on the seat of election, i.e., just above the cusps. In all the other cases of this series examined microscopically there existed pathological processes in the aortic wall. The effect of a continuous high blood pressure

in the aortic arch is apparently of the greatest importance; there results a dilatation of the vessel with a marked thinning of the walls proximal to the coarctation, even to parchment paper thinness. There may be marked changes in the media consisting of interruption and diminution of the elastica with an increase of fibrous connective tissue; hyaline and frequently fatty degenerative changes are found. A great majority of these cases showed a dissecting aneurysm which ruptured secondarily into the pericardial sac or into an adjacent viscus.

Inflammation.—Intrinsic inflammatory processes, syphilitic and non-syphilitic, are not uncommonly the basis for rupture of the aorta. The gradual destruction of both elastica and muscle elements of the media, with subsequent fibrous connective tissue scarring and intimal sclerosis, and later dilatation of this weakened structure to aneurysmal proportions and rupture are frequent in syphilitic aortitis. Because of the apparent welding of the neighboring laminae by the connective tissue reaction in syphilitic mesaortitis, Klotz and Simpson[5] feel that this disease plays no part in the production of true dissecting aneurysm. Tyson,[24] Tidmarsh,[25] Lifvendahl,[15] and Gsell[26] report cases of dissecting aneurysm and rupture of aortas showing typical luetic mesaortitis without the usual marked dilatation of the aortic lumen.

Infections of the aorta, other than syphilitic, resulting in rupture are comparatively rare. The localization of infectious emboli in the aortic wall entering by way of the vasa vasorum, with abscess formation and at times mycotic aneurysmal dilatation and rupture has been described. Infectious endarteritis varying in its bacteriological findings occasionally develops in a *locus minoris resistentiae* afforded in the vicinity of a coarctation. A favorable nidus is provided here where the aorta is generally dilated, deformed and atheromatous. Poynton and Sheldon[27] have described such a case and collected four from the literature. Reifenstein,[28] Smith and Hausmann,[29] Libman,[30] and Narr and Johnson,[31] have described similar cases with rupture.

It is rather surprising that the extensive muscular degeneration resulting from rheumatic aortitis as described by Pappenheimer and von Glahn,[32] Sacks[33] and others does not result in rupture of this large vessel, but it undoubtedly does in smaller vessels. The rheumatic inflammatory process does not destroy the elastica, wherein lies the strength of the aorta. It will be noted that rheumatic fever cannot be excluded as the cause of rupture of the aorta in a case of Lifvendahl.[15] The importance of infectious lesions in the destruction of the aortic media is vouched for by Wiesel[34] who noticed the presence of peculiar focal necrosis in the vessel wall of young individuals dying of acute infections. Klotz[35] believes that multiple bacterial emboli are the most important factor in the medial degeneration of arteriosclerosis. Many other authorities, including Gsell,[26] Erdheim,[36] Schede,[37] Stoerck and Epstein,[38] Klotz,[39] Duff,[40] and Bailey,[41] have suggested the

possible importance of bacterial toxins in the degenerative processes which may eventually terminate in rupture of the aorta.

Degeneration.—Intrinsic degenerative changes in the aortic wall leading to its rupture may be divided into the (a) arteriosclerotic and (b) medial degenerative types.

(a) Of the eighty cases of ruptured aorta collected by Peacock,[1] forty-two had arteriosclerosis. MacCallum's[42] five cases all showed advanced arteriosclerosis. Similar cases of Gager,[43] Gallagher,[44] Thorpe,[45] Sheldon and Dyke,[46] Tyson,[24] Maitland,[47] Strickland,[18] Lifvendahl,[15] Kaufman,[48] and many others stress the importance of arteriosclerosis as a cause of spontaneous rupture of the aorta. A great majority of the aortic tears occurring after the age of forty are due to arteriosclerosis. Adami[49] cites Aschoff, Klotz and Foster in describing physiological changes of the aorta, an increase in elastic fibrils in number and size up to thirty-five years of age when their development becomes stationary for fifteen years. After fifty years there is noticed a slow progressive atrophy of the elastica as well as fatty degeneration of muscle fibers. Small calcareous granules are seen in some of the cells followed by necrosis and their complete absorption. The remaining elastic elements are thus allowed to stretch, losing their wavy appearance and elastic quality. Mackenzie has demonstrated a gradual disappearance of capillaries with advancing age resulting in degenerative changes in the places with poorest blood supply. The aorta of a child is quite elastic, and its lamellae are firmly bound together so that they cannot be separated. On the other hand, the aortas of old age lack elasticity and possess an unusual dryness and friability so that their walls can occasionally be separated without difficulty.

Among the many etiological requirements of arteriosclerosis perhaps those of greatest importance are: (a) increased functional demand, (b) injury to the wall by infectious and toxic influences, (c) nutritional and metabolic disturbances, and (d) familial and hereditary predispositions. These subjects we cannot enter upon here.

The arteriosclerotic process may have its onset in fibrous connective tissue proliferation of the intima, with subsequent degenerative changes of a fatty and hyaline nature and with calcium and cholesterin crystal deposits, necrosis, ulceration and rarely true bone formation. The media may participate with fatty degeneration, atrophy and necrosis of both muscular and elastic elements, especially in areas underlying intimal plaques. Later chalky connective tissue masses replace the lost medial elements. Perivascular fibrous connective tissue proliferation with round cell infiltration may be difficult to distinguish from a syphilitic lesion. At post-mortem examination the eggshell-like intimal layer may crack and split away on the slightest provocation. It is surprising that dissecting aneurysm with rupture or with re-

entrance of the lumen and healing (Hall[50] and Cleland[51]) is not more common, considering the number of severely atheromatous aortas seen at the autopsy table.

It should be pointed out that a primary intimal tear is not always a complement necessary for rupture. Tyson,[24] citing a few cases of his own and of others, stressed the point that dissecting aneurysms begin by hemorrhage from the vasa vasorum as a result of medial degeneration and that a tear in the intima of the aorta is not a necessary factor in the formation of such aneurysms. Furthermore he feels that when intimal tears do occur, they are probably secondary to the development of the aneurysm.

(b) Of the many causes for rupture of the aorta, that due to primary degeneration of the media is of the greatest pathological interest. There may be several types of medial degeneration, including (1) that of Gsell and (2) that of Babes and Mironschu. Of these that of Gsell stands out as an accepted histological entity. Gsell[26] first described the condition in 1918 and later Erdheim,[36] reporting two cases, gave it the name "medio necrosis aortae idiopathica cystica." Since then about twenty cases in all have been reported by various authors, including Klotz and Simpson,[5] Tyson,[24] Moritz,[14] and Levinson.[57] This degenerative change of the media is not necessarily associated with any atherosclerotic changes in the intima and occurs in young adults as well as in older people. It is characterized by necrosis of the media and at times of the intima. Usually it is found only in the aortic arch but is especially marked in the ascending portion where the rupture and dissection of the media invariably begin. Occasionally the whole aorta is involved. Practically all deaths in this condition were due to cardiac tamponade due to secondary rupture into the pericardial sac. Histologically there is a bland patchy or bandlike necrosis, most marked in the middle portion of the media, affecting first the smooth muscle cells, with karyorrhexis and then complete necrosis, leaving a pale acidophilic homogeneous material. Later the more resistant connective tissue cells and elastica stain poorly, fragment and gradually fade into the same homogeneous light pink staining débris. Moritz[14] following Schultz describes this tissue as chromotrophic substance and believes that it is deposited about the elastic fibrils and predisposes to their degeneration. The aorta may rupture at this stage or the degeneration may proceed to cyst formation. Erdheim[36] describes a healing process in which the cystic areas contain scattered stellate connective tissue cells (not scar tissue), or the healed areas may liquefy to form serous cysts. The process from the onset is free from inflammatory cell infiltration, there may or may not be fat droplets in the smooth muscle cells and about the elastica. Moritz[14] found finely granular deposits of calcium in the chromotrophic substance.

The pathogenesis of medial necrosis is debatable. Tyson[24] describes occlusion of the vasa vasorum, due to intimal proliferation, with medial degeneration the result of nutritional disturbances. Klotz,[35] Moritz,[14] and others agree that the necrosis is not to be explained in this manner. Moritz[14] found chromatrophic substance in six of seventy adult aortas and suggests an involutional or senescent change. Theories of exogenous poisons (adrenalin and nicotine), poisonous products of metabolism and vitamin deficiency have been advanced. Duff[40] has demonstrated medial changes in animal experiments following the injection of diphtheria toxin; these are said to be very similar to the patchy medial destruction in man. Unusually frequent or severe infectious diseases have not been elicited in the histories of these frequently healthy appearing individuals with medial necrosis. The solution awaits further investigation.

Babes and Mironschu[53] describe as a disease entity, "Mesarteritis dessecans," a very unusual type of degeneration in the aorta. Their case is from a fifty-one-year-old woman who died suddenly of a ruptured aorta. In the media of this vessel were small foci of thickened elastic fibers enclosing spindle-shaped clefts. There were systems of confluent clefts, where the elastic fibers were torn, and about these were large mononuclear cells and small hemorrhages; here and there were areas of fatty degeneration which at first were localized exclusively in elastic fibers. The heavier lamellae were enclosed in fat, while the smaller fibers contained fat, and this increased at the expense of the elastic tissue. There were some calcareous changes, connective tissue proliferation, round cell infiltration about the vasa vasorum and sclerotic changes in the intima.

In reading the descriptions of the microscopic examinations of reported cases of rupture of the aorta one finds instances which do not fit into the classification noted above. Apparently there are other less distinct types of degeneration of the aorta. There are also a number of spontaneous ruptures reported where the authors vouch that there were no gross or microscopic changes (Kaufman,[48] Richey,[20] Loeffler,[17] Paseckis,[54] Suss,[55] Arenberg,[56] and others).

CASE REPORT

The patient was a married physician, twenty-nine years old. He was admitted to Research Hospital, service of Dr. Robert C. Davis, complaining chiefly of severe precordial pain of four days' duration. He had had smallpox at six years, tonsillitis five years ago, occasional attacks of grip, and pertussis in the summer of 1932. He had been a rather heavy drinker of alcoholic beverages and had been known to indulge in breathing ether and chloroform vapors. His systolic blood pressure had varied from 130 to 170 mm. during the last few years. His wife and two children were in good health; the family history was essentially negative.

The patient had apparently been in good health until seven days before his death when, while shaving, he had a sudden extremely sharp pain over the precordium followed by vertigo, dyspnea, pallor and marked weakness. In spite of large doses

of opiates, the pain remained severe through the night. The next day he rode 200 miles in a car and did some dancing. During the next two days he was confined to his bed, had four or five mild chills with fever, and developed petechiae in the left axilla. On admission to the hospital he was orthopneic and extremely restless. He had a nonproductive cough, vertigo, general aching and marked perspiration. His respiratory rate gradually increased during his three days in the hospital from 20 to 45 per minute. The pulse remained about 125 and his temperature was irregular in its variation from 97° to 101° F. The physical examination was essentially negative except for a moderately enlarged heart, with a precordial thrill and a harsh blow filling systole and most of diastole, heard over the entire chest but best at apex. There were a few blotchy fading petechiae in the left axilla. Blood pressure was 134/70 mm. Radiological examination indicated increased fluid in the pericardium and some cardiac hypertrophy. Routine blood and urine analyses were essentially negative. The Wassermann test was negative. Repeated blood cultures showed no growth. Electrocardiographically there were marked right ven-

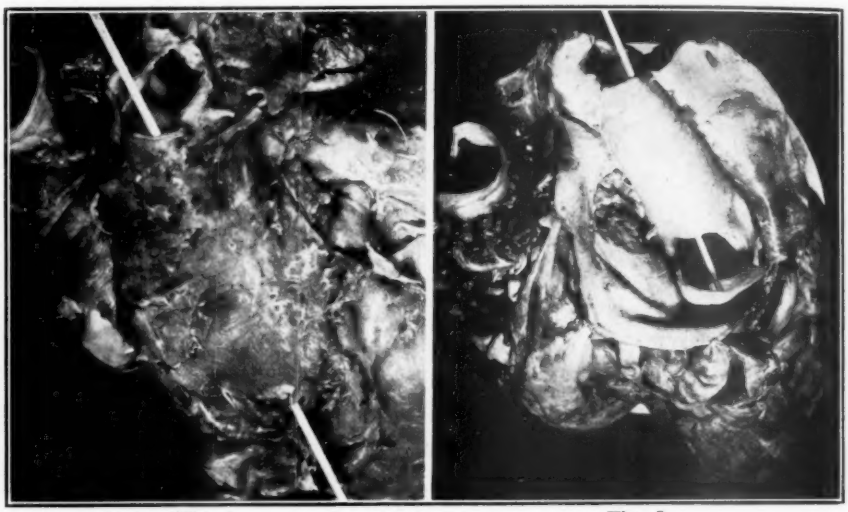

Fig. 1. Fig. 2.

Fig. 1.—Small tear of adventitia of aorta within a centimeter of its base. Probe passes through this tear into dissecting aneurysm.

Fig. 2.—The outer wall of the dissecting aneurysm opened and edges spread to show the separation of adventitia from media in lower portions and separation of several layers of media in upper portion, as well as horseshoe rent of intima and media a few millimeters above the aortic valves.

tricular predominance, notched P_2, negative P_3 and an increase in the ventricular conduction time. The patient died suddenly on his seventh day of illness.

Autopsy.—The *heart* weighed 500 mg. The pericardial cavity contained approximately 500 c.c. of dark red, friable blood clot. The pericardial surfaces were covered by flakes of fresh fibrin which were easily torn away from the surface. There were no fibrous adhesions and no gross evidence of an acute inflammatory process. A small tear, measuring about 0.6 cm. in diameter, was found in the adventitia of the aorta within 1 cm. of its base. Further exploration revealed a communication through this hole directly into a dissecting aneurysmal cavity located between the adventitia and media in places and between the outer layers of the media in others, extending entirely around the aorta excepting for 2 cm. on the concave aspect where the layers had not been separated, and extending up the main branches of the

aortic arch for a short distance, involving the entire aortic arch and about 5 cm. of the thoracic aorta at which point it re-entered the lumen of the aorta. There was a horseshoe-shaped rent through the media and intima on its anterior and right lateral aspect, the two points beginning within a few millimeters of the level of attachment of the aortic valves, extending 3 cm. upward on one side and 2 cm. on the other, the two lines communicating by a curved line about 3 cm. long. The exposed inner surface of the adventitia was a dark red color and showed deposits of fibrin. The intima showed a few small scattered yellowish plaques located in the first 2 cm. of the ascending aorta, the largest of which measured 3 mm. in diameter. The aorta measured 9 cm. in circumference at its valves. The aortic end of the ductus arteriosus was patent, into which a 1 mm. probe could be inserted to the point of occlusion in the wall of the pulmonary artery. There was a definite smooth constricting band located at the level of the left subclavian artery (coarctation); at this point and beyond it the aorta measured 4.5 cm. in circumference. The aortic valves showed rather extensive fenestration, and there was a slight increase in their fibrous tissue. The mitral valve showed a definite thickening of its edges due to

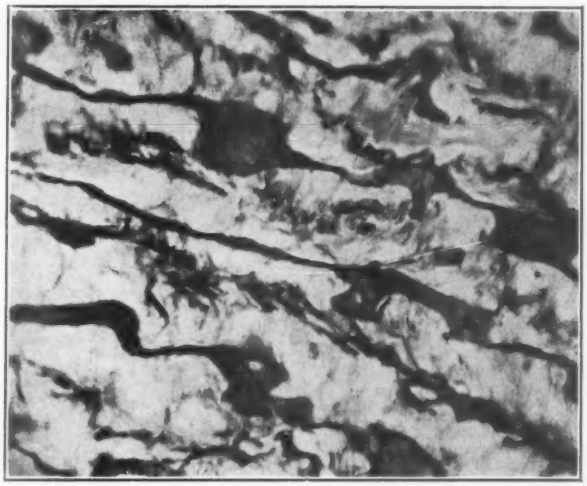

Fig. 3.—Weigert's elastic stains showing bulbous swellings of elastica and degeneration of muscle fibers.

connective tissue proliferation and firm translucent nodules along the entire edge, some measuring 2 mm. in diameter. There was possibly slight shortening of the chordae tendineae of this valve. The left ventricle was moderately dilated as was the left auricle. The remaining two valves showed no lesions. The endocardial surfaces were not changed excepting for a reddish blotchy discoloration underlying the endocardium of the right auricle in the immediate vicinity of the ruptured aorta. The myocardium of the left ventricle was considerably hypertrophied and had a normal consistency; it showed no fibrosis. The coronary arteries showed a moderately advanced atherosclerotic process, with calcium deposits, for a distance of about 6 cm. from their onset, but no point of occlusion.

The *lungs* showed a moderate congestion of their lower lobes and were otherwise normal. The *liver* weighed 2150 grams and was moderately congested. The *spleen* weighed 240 grams, its pulp was soft, congested and granular. *Lymph nodes* in mesentery, mediastinum, and especially those at the base of the heart, were moderately enlarged, frequently measuring 1.5 cm. in diameter. The other viscera showed no gross changes.

Microscopic Examination.—Heart: Multiple sections taken from this organ showed the muscle fibers well stained and their cross striations distinct. The nuclei showed no changes. There was slight increase in the amount of interstitial connective tissue. The pericardium showed slight thickening, possibly due to edema, and also had a scattered lymphocytic and plasma cell infiltration. Occasionally small flakes of fibrin were seen on the pericardial surface. Sections through the coronary arteries showed an advanced sclerotic process characterized by marked intimal thickening throughout the circumference of the vessel, which appeared as degenerated or necrotic tissue arranged in a bizarre manner and taking a slight pink stain. This degenerative change involved the entire intimal layer of most of the circumference and the media, except for a few muscle fibers in its outermost layers.

Aorta: Sections taken from the immediate vicinity of the rupture showed an extensive retrograde process involving especially the central portion of the media,

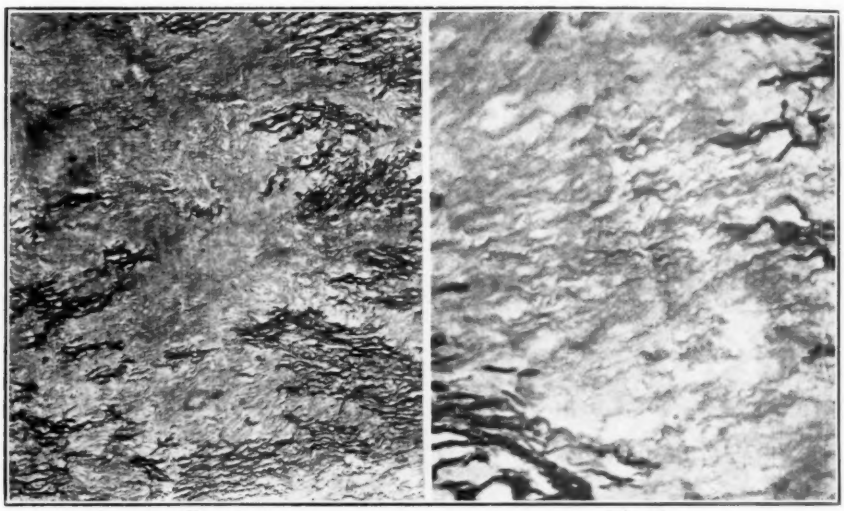

Fig. 4. Fig. 5.

Fig. 4.—Weigert's elastic stain (low power). Medial necrosis with loss of elastic and muscle fibers and their replacement by homogeneous and fibrillar material.

Fig. 5.—High power magnification of Fig. 4.

where there was a bandlike necrosis. In places this extended to involve the entire media and intima, and in others it was patchy in its distribution. These very markedly involved areas were characterized by complete loss of cells, there remaining only a very light pink staining shadow of a few of the former cells and elastic fibrils. As stated, this necrosis of the tissues was evidenced primarily in the medial portion of the media; however, in the same section one could notice a similar process diffuse and patchy in its distribution, involving the entire media, and at times the intima, throughout the sections taken from the ascending portion of the aortic arch. There was a marked diminution in the number of cell nuclei and elastic fibrils throughout the media, including the areas not necrotic. Sections taken from the descending portion of the aortic arch showed a much less involved tissue; however, there was still a central band of apparently necrotic medial cells of rather narrow breadth. Sections from the thoracic aorta showed an entirely normal cellular and elastic structure. The vasa vasorum in both the adventitia and media showed only sparse cellular infiltration, amounting to an occasional lympho-

cyte or monocyte. This infiltration was more extensive in the immediate region of the dissecting aneurysm. In a few sections where the dissection was between the media and adventitia one found definite long cracks running in the longitudinal bandlike necrotic area of the media. Lining the aneurysmal walls was a rather thick layer of fibrin, and at times one would find fibrin in the cellular tissues in the immediate vicinity of the aneurysmal sac as well as small accumulations of red blood cells. Weigert's elastic stains showed almost complete loss of the staining properties of fibers in the regions of necrosis described above. The elastic fibers in other regions of the arch were badly fragmented and frequently showed bulblike swellings. Fat stains showed only rare small fatty deposits anywhere. Sections taken a short distance from the dissecting aneurysm showed no hemorrhages and no neutrophilic infiltration. There was no connective tissue proliferation in any of the three layers. Cyst formation, occlusion of vasa vasorum or attempts at healing could not be found.

Microscopic study of other organs revealed a chronic passive congestion of the lungs and spleen but no other significant changes.

CONCLUSION

We consider this a typical case of idiopathic medial necrosis with rupture of the aorta. As is usually the case, it occurred in a young, apparently healthy and active adult, having had no unusual or severe illness in his past. In this case there had been considerable dissipation, with an excessive use of alcohol, nicotine, ether and chloroform. An etiological significance of the healed rheumatic lesion of the mitral valve is considered unlikely, also a mild degree of coarctation may have been a contributing factor by increasing the blood pressure proximal to the constriction. Except for the extensive degenerative changes in the coronary arteries other blood vessels were not affected. Evidence of an infectious process in any organ is lacking. In this case, as is almost invariably true in the reported cases, the intimal tear was in the ascending arch, and the patient died of cardiac tamponade when the dissecting aneurysm ruptured.

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DESCRIPTION OF A MON-AURAL DIAPHRAGM TYPE OF STETHOSCOPE WITH DISCUSSION OF ITS SPECIAL FIELD OF USEFULNESS*

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IT IS probable that marked variations in sound perception exist in individuals with apparently normal hearing. These, apart from changes in the auditory apparatus, may be due to certain atmospheric conditions, fatigue, and congestion of the upper respiratory tract. Because extrinsic influences are variable it is difficult to appraise the efficiency of hearing, especially in the perception of fine gradations. This is in contrast with purely mechanical devices in which transmission and reception of sound are controlled and studied with nice precision.

Since few individuals hear exactly the same under all conditions, questions arise as to the efficiency of instruments for magnifying and conveying vibrations which are heard as sounds. In stethoscopes the comparative value of the so-called bin-aural bell type and the diaphragm type has been widely discussed. The accuracy of the "bell" for the study of vesicular and loud bronchial sounds, râles and low pitched, rumbling, crescendo heart murmurs is recognized. Differences of opinion exist chiefly in the elicitation of high pitched, faint, blowing heart sounds of aortic insufficiency and faint, high pitched "bronchial" respiratory sounds. These, according to some observers, are heard satisfactorily with the diaphragm model. In order to obtain the advantages of both types the "bell" and "diaphragm" have been incorporated in the same instrument. This is convenient and satisfactory for general use but criticisms have been noted. It has been found especially that reception from the diaphragm sector is less distinct than from the single diaphragm model, and the bell sector gives marked exaggeration of the finer tones. This is attributed to the lack of insulation between the two sectors and to one part's acting as a resonator for the other part.

In reviewing the writings of early clinicians, especially Laennec, one is impressed with important observations made with the ear alone or the simple stethoscope. It may appear in comparison that the refined instruments of the present day are not giving all the information that can be obtained. This was emphasized by L. A. Conner[1] in

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an interesting paper on the limitations of the stethoscope. He pointed out that sounds which are faintly heard or missed entirely may be heard clearly and sharply with the ear alone. A similar view was expressed by L. F. Flick[2] who has observed in studying diseases of the lungs for over fifty years that soft blowing bronchial sounds existing in the presence of vesicular sounds are lost through the bin-aural stethoscope but with practice may be heard clearly with the mon-aural type.

It appears from these considerations that one stethoscope may not be suitable for all examinations. The ear alone, as pointed out by Conner, should be used far more frequently than is done by the younger physicians. Due to certain objections, which are largely questions of delicacy, hygiene or inconvenience, the use of some mechanical device is often required.

In the development of the stethoscope to be described, an attempt has been made to utilize, so far as possible, the mechanisms of air and bone conduction which are features of the ear alone and the mon-

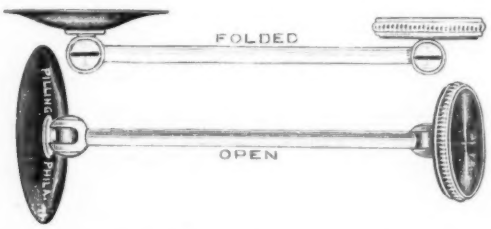

Fig. 1.—The upper illustration shows the instrument with the ear and chest pieces folded (for carrying) against the stem. In the lower illustration the ear and chest piece assemblies are open for use. The ball-and-socket joint construction is shown.

aural stethoscope. The effects of metal, rubber and wood conducting media were especially studied. Soft rubber was eliminated because of its damping effect. Metal was selected in preference to wood because it has peculiar values in transmitting sounds with a ringing quality. It is generally as satisfactory as wood for the transmission of other sounds and is especially suitable for good workmanship.

DESCRIPTION OF A METALLIC MON-AURAL DIAPHRAGM STETHOSCOPE

A standard diaphragm type of chest piece (Bowles) was modified as follows: (Fig. 1.) The weight of the chest piece was reduced one-sixth, the clefts were obliterated, the dome increased to 3.5 mm. in depth. The chest piece diameters of 2.5 and 4.5 cm. (two sizes) were retained. The opening between the chest piece and the stem was bored to a diameter of 2 mm. A circular base 1.5 mm. in width was ground for contact with the diaphragm. A hard rubber ring was screwed to the circular base and holds the diaphragm flush with the base. The rubber ring provides a warm surface for contact with the chest wall and when removed the instrument is converted into a "bell" stethoscope. The stem (12 cm. in length) was made from heavy brass tubing, the lumen was bored to a diameter of 1.5 mm.

One end of the tubing was connected with the chest piece by means of a ball-and-socket joint, the other end, in a similar manner, to the ear piece assembly. The ear piece consists of a hard rubber disc 6.5 cm. in diameter molded to fit over the lobe of the ear. The ball-and-socket joints have counter sunk construction which provides an opening through the joints when the chest and ear pieces are turned to any angle up to 30°. Because of this mechanism the instrument can be adjusted

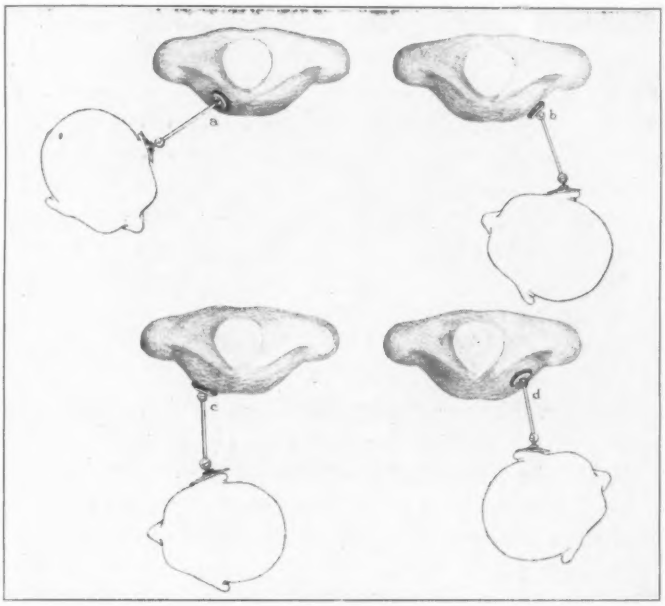

Fig. 2.

Fig. 3.

Figs. 2 and 3.—Showing the various positions of the examiner's head when studying remote parts of the chest.

easily for the study of remote parts of the chest. Tension springs are placed in the joints to prevent accidental turning of the ear and chest piece assemblies during the examination. For carrying in the pocket the ear and chest pieces may be "folded" against the stem.

As in the evaluation of all stethoscopes, the question of individual preferences as well as the influence of physical laws must be considered. As compared with the bin-aural diaphragm type in the study of heart murmurs there is less distortion of sound and usually finer definition. It is useful especially in the eliciting of aortic murmurs, and the results are comparable with those obtained with the ear alone. Certain accentuating sounds existing in the presence of humming or blowing noises may be heard with striking clearness. Amplification is usually greater than in the mon-aural bell type. In studying the lungs a most helpful feature is the transmission of soft blowing bronchial sounds and râles with a ringing quality. Clinical trials do not suggest that the instrument should replace other stethoscopes or the ear alone but rather that it may be employed as a supplementary instrument.

Remarks by Dr. Thomas McCrae.—It has been interesting to compare this mon-aural stethoscope made of metal with the usual one made of wood. The transmission of sounds is somewhat different and on the whole the mon-aural metal stethoscope impresses me as being more useful than the wooden one. It is unfortunate for our education in auscultation that the mon-aural stethoscope is so rarely used. After all the only advantage of the bin-aural stethoscope consists in its being more convenient. The mon-aural instrument transmits certain sounds much better. No one should regard his education in the practice of auscultation as complete until he has learned to use a mon-aural stethoscope. For the auscultation of the heart it has many advantages; one feels the impulse at the same time as one hears the sounds. One has to learn to disregard sounds which enter by the unengaged ear, just as the impressions received by the eye which is not used with a microscope with a single eyepiece are not perceived. The other eye is kept open but the images do not register. It has often interested me to see the surprise shown by a man who uses a mon-aural stethoscope for the first time, as many regard it as an antique instrument of historical interest only and markedly inferior to the bin-aural form; a trial usually shows the contrary. If you are one of the unfortunates who has to close the other ear to hear what is transmitted by the mon-aural stethoscope, then, of course, it is not so useful.

While Dr. Gordon has emphasized the employment of this instrument in the auscultation of the heart, my feeling is that for the study of certain pulmonary sounds it has distinct advantages. One cannot describe the differences in sounds; only an individual trial can demon-

strate them. The use of the mon-aural instrument is well worth while by every one who wishes to improve himself in auscultation. It would be a good thing if every interne had to use a mon-aural stethoscope for a time. It may be added that many of us forget that direct auscultation is often valuable. It should be used more than it is.

COMMENT

The failure of the bin-aural stethoscope to transmit effectively the soft blowing high pitched heart murmurs and certain pulmonary sounds has been noted. It has been observed in contrast that these may be heard clearly and sharply with the ear alone or with a mon-aural stethoscope. A mon-aural diaphragm type of stethoscope which utilizes the mechanisms of air and bone conduction and is easily adjusted for the special examination of remote parts of the chest is described. With practice the instrument is especially effective in transmitting soft blowing and ringing sounds and certain other phenomena not clearly heard with the bin-aural "bell" or "diaphragm" stethoscope.

The instrument is manufactured by the Geo. P. Pilling and Son Company, Philadelphia.

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REPORT OF A CASE OF PAROXYSMAL VENTRICULAR FIBRILLATION IN RELATION TO QUINIDINE THERAPY*

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THE beneficial effect of quinidine sulphate in the treatment of tachycardias of ventricular origin is well recognized. There are numerous reports of cases in which the ventricular tachycardia has been stopped or the frequency of the attacks greatly diminished by its use. This subject has recently been well reviewed by S. A. Levine and Fulton.[1]

The relation of quinidine sulphate administration and ventricular fibrillation is not so clear, primarily because of the rarity of the condition and the difficulty in making clinical observations as to the efficacy of such treatment. Kerr and Bender[2] report a case in which attacks of ventricular fibrillation occurred when quinidine sulphate was administered, and Davis and Sprague[3] report death from ventricular fibrillation in the course of quinidine therapy. Dock,[4] however, reports a case in which a maintenance dose of quinidine prevented attacks of paroxysmal ventricular fibrillation. Furthermore, H. D. Levine[5] recently demonstrated in the experimental animal that quinidine has an inhibitory effect on ventricular fibrillation and makes it more difficult for the irregularity to develop than in the control unquinidinized animals.

This case is being reported because of the comparative rarity of paroxysmal ventricular fibrillation, and as an illustration of the effect of quinidine sulphate in the condition.

CASE REPORT

J. D. (Med. 41316), a sixty-year-old, white, unmarried janitor was first admitted to the medical service of the Peter Bent Brigham Hospital on June 23, 1932. He complained of "fainting spells."

The family history was not remarkable except that one brother and one sister died of cardiovascular disease. The past history was negative. There was no history of rheumatic fever or syphilis.

The present illness began two years before when he first noted a feeling of fullness in the epigastrium which seemed to rise and cause a sensation of pressure in the throat. He thought he had "indigestion." Following one of these attacks he lost consciousness for a few minutes. He then consulted his physician who discovered hypertension and put him on a diet. No digitalis was given. His attacks of discomfort decreased in number, but during these two years he had two more "fainting spells." Four months before entry he noticed that the attacks of fullness in the epigastrium were accompanied by some numbness and tingling in the left arm.

*From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.

On the day before admission he experienced such an attack and that night, while walking from one room to another, he suddenly became very dizzy and faint and fell to the floor. According to family reports he was unconscious for about fifteen minutes. He then remained in bed, but on the morning of entry had another attack of syncope shortly after awakening. There were two more "fainting spells" before admission that afternoon. He denied having experienced any precordial pain or palpitation and between attacks had noted no dyspnea, orthopnea or ankle edema. He had continued his work as a janitor in a lithographing plant until he was laid off two months before admission.

Physical examination revealed that the patient was moderately obese and in no apparent discomfort. The optic fundi showed moderate evidence of retinal sclerosis. The heart was moderately enlarged, with a diffuse apex impulse. The left border of dullness was 11.5 cm. from the midsternal line; right border of dullness was

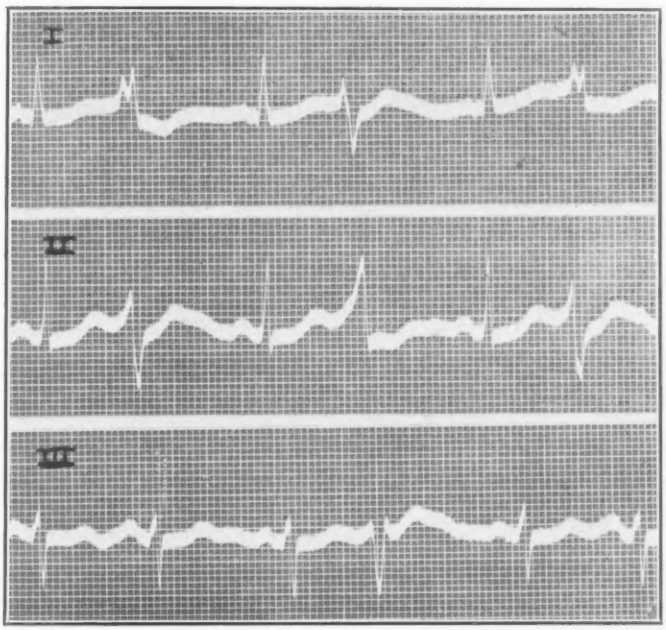

Fig. 1.—(Leads I, II, and III) Taken shortly after admission on June 23, 1932. Showing the occurrence of frequent ventricular extrasystoles, at times simulating coupling.

just outside the right sternal margin. At the apex the heart sounds were of good quality, but at the base they were somewhat distant. There was a soft systolic murmur at the apex. The rhythm was regular except for occasional extrasystoles and the rate was 80 per minute. The lungs were clear and the liver was not enlarged. No edema of the extremities or sacrum was present. Blood pressure was 150 mm. systolic and 80 mm. diastolic.

Laboratory Findings.—Blood—Hgb. 74 per cent (Sahli), R.B.C. 4,410,000 per c. mm., W.B.C. 18,600 per c. mm. of which 95 per cent were polymorphonuclear cells. Urine—very slight trace of albumin. The sediment showed numerous hyalin and granular casts. The Wassermann and Hinton reactions of the blood serum were negative. Blood urea nitrogen 17.9 mg. per cent. Phenolsulphonephthalein excretion in two hours and ten minutes (intramuscular injection) was 55 per cent in 80 c.c. of urine.

A seven-foot roentgen-ray examination of the heart thirteen days after admission showed enlargement both to the right and to the left with a rather blunt ventricle suggesting hypertrophy. The aorta was tortuous but not dilated. Fluoroscopic examination showed a regular vigorous beat with a fairly marked expansion of the aorta. The cardiac measurements were: Midline to right border 6.1 cm., midline to left border 9.3 cm., great vessels 5.5 cm., internal diameter of the chest 29.8 cm.

Course During the First Admission.—On the afternoon and evening of admission the patient had three attacks of syncope and numerous attacks of transient vertigo. Clinical observation disclosed that the normal rhythm was never free of occasional extrasystoles, and preceding an attack of vertigo these would increase in number

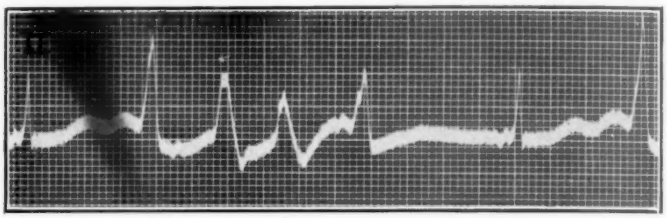

Fig. 2.—(Lead II only) Showing increasing numbers of extrasystoles which generally preceded attacks of ventricular tachycardia.

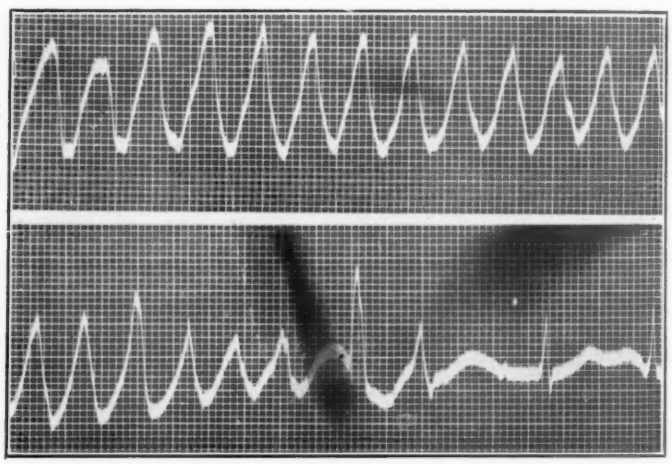

Fig. 3.—(Lead II only.) A continuous strip and shows approximately the last half of an attack of ventricular tachycardia with recovery and return to normal rhythm. The total duration was ten seconds and the rate reached 214 per minute. It was during these attacks that the patient felt agitated and dizzy and complained of epigastric fullness.

so that the rhythm became very irregular. This would finally lead to a short tachycardia lasting from seven to eleven seconds during which the rate was 180 to 200. At this time the patient became very agitated, dizzy and moderately cyanotic. He complained at such times of a feeling of fullness in the epigastrium rising to his throat and causing a sensation of pressure there. These were similar to attacks he had had before entering the hospital. The tachycardia stopped abruptly and was followed by a diminishing number of extrasystoles; the heart gradually returning to its normal rate of about 80. Several of these attacks of tachycardia with the transition to and from normal rhythm were recorded by the electrocardiograph.

The syncopal attacks started in the same way except that after a short tachycardia the heart sounds and pulse disappeared. At this point his breathing would become stertorous and his color livid. The eyes were rolled back and he would thrash about on the bed. The duration of the attacks varied from fifty seconds to three minutes, and during the longer periods respirations ceased after approxi-

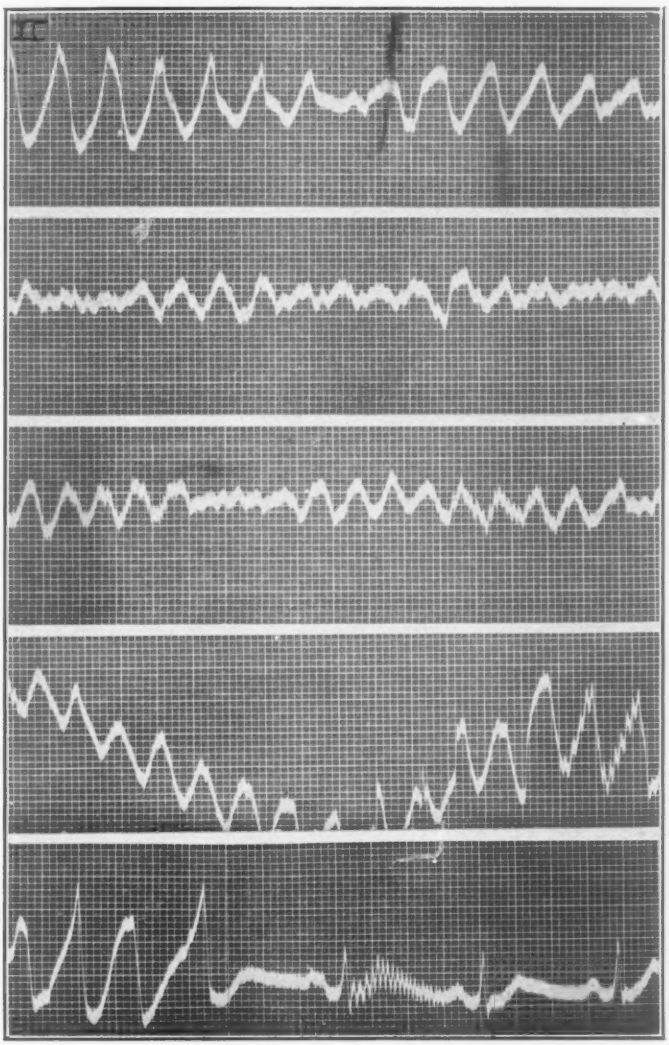

Fig. 4.—(Lead II only) shows sections from an attack of ventricular fibrillation. The first strip shows the end of the tachycardia which preceded the fibrillation and the beginning of the fibrillation. The second and third strips were picked at random and are typical of the fibrillation which persisted for approximately ninety seconds. The fourth and fifth strips are continuous and show the end of the attack with a change to a short run of tachycardia and then the sudden reversion to a normal rhythm.

mately one and one-half minutes. The attacks would end with the return of the heart sounds which were pounding in character and very rapid at a rate of approximately 200. The rate slowed after a few seconds with a progressively diminishing number of extrasystoles. Following apnea the respirations would return, starting

with a few gasps. There would be a concomitant improvement in color, and the patient generally returned to consciousness, usually remarking about the severity of the attack. On a few occasions he remained disoriented for as long as one to two hours after the attack.

The third attack after admission was recorded completely by the electrocardiograph, and the oral administration of quinidine sulphate was then instituted. In the twenty-four hours before the medication was started, the patient had had seven syncopal attacks.

That evening he was given two doses of 0.3 gm. each of quinidine sulphate, the last at midnight. On the second day he was given 0.3 gm. at 10 A.M. and 0.5 gm. at 2 P.M. and 6 P.M. He had two short syncopal attacks that afternoon, but that night at 2:40 A.M. he had a severe attack from which he did not completely recover

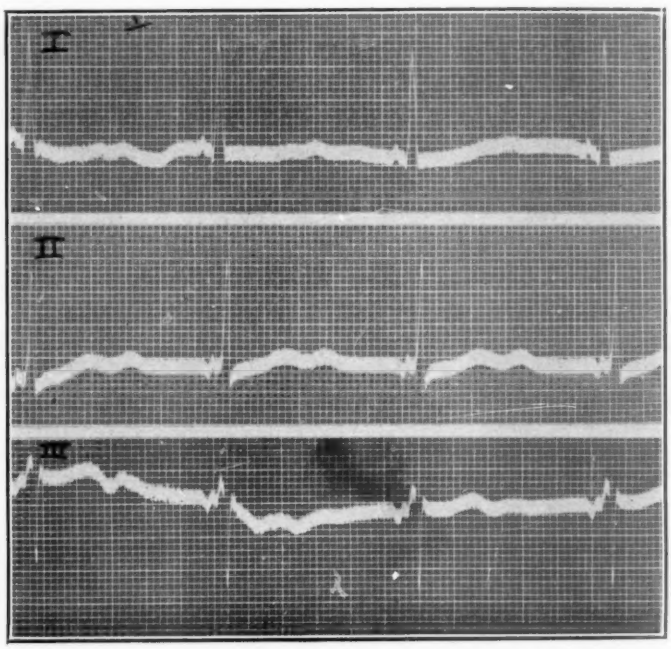

Fig. 5.—(Leads I, II and III) Taken during the second hospital admission when the patient was receiving large doses of quinidine (0.5 gm. 5 i.d.). Showing nodal rhythm.

for two hours. The heart rate did not return to normal, but frequent extrasystoles kept it irregular at a rate of 120 per minute, and the patient remained agitated and markedly disoriented for approximately one hour. He then partially recovered and was given 0.008 gm. of morphine sulphate hypodermically. This quieted him, and after another hour he returned to sleep.

It was then decided to decrease the time interval between the last dose of quinidine in the evening and the first dose in the morning, and on his third day the patient received 0.5 gm. of quinidine at 10 A.M. and 0.4 gm. at 2 P.M., 6 P.M. and 10 P.M. On the fourth day he was given 0.4 gm. five times, the first dose at 6 A.M. and the last at 10 P.M. There were no further syncopal attacks during the hospital stay, and on the sixth day reduction of the dosage was started. On the eighth day he was allowed out of bed, and by the tenth day he was receiving only 0.3 gm. of quinidine three times a day at 8 A.M., 2 P.M. and 8 P.M. On the fifteenth day this was reduced to 0.3 gm. twice a day at 8 A.M. and 8 P.M.

By the tenth day his white blood cell count had fallen to 6,550 per c. mm. and his urine had cleared completely. His temperature which was elevated to 99° F. in the afternoon during his first week in the hospital remained below 98.6° F. thereafter. The blood pressure showed a gradual elevation and on the fifteenth day was 174 mm. systolic and 88 mm. diastolic.

The patient was discharged from the hospital eighteen days after admission feeling quite well. He was advised to take 0.3 gm. of quinidine sulphate at 8 A.M. and 8 P.M. every day.

Interval history.—He returned five weeks after discharge to report that on a régime of limited activity he had had several bouts of "gas" and one attack of syncope. He had been taking his quinidine regularly. The bouts of "gas" were essentially the fullness in the epigastrium ascending to the neck as described before, associated with numbness in both arms and transient vertigo. The syncopal attack had occurred while he was asleep, and according to his family who were aroused by his stertorous breathing, it lasted only a few minutes. He felt perfectly normal after the attack. Physical examination at the time of the visit showed no change. The heart was slow and regular except for occasional extrasystoles. The blood pressure had risen to 200 mm. systolic and 96 mm. diastolic. Because of the syncopal attack he was advised to increase his daily dose of quinidine to 0.3 gm. three times a day to be taken at 8 A.M., 2 P.M. and 8 P.M. An electrocardiogram taken at that time showed nodal rhythm and left ventricular preponderance. The rate was 60.

His next visit was three weeks later (two months after discharge). He had had no further syncopal attacks. His heart rhythm was regular, rate 80.

He felt well until four and a half months after discharge when on November 23, 1932, he had a syncopal attack shortly after awakening. He remained in bed, but had three more during the day and was advised by his physician to reenter the hospital.

Summary of the Second Hospital Admission.—Physical examination was essentially as before with the blood pressure at 195 mm. systolic and 68 mm. diastolic. Examination of the heart showed frequent extrasystoles with occasional regular occurrence causing apparent coupling. Several short runs of eight to ten rapid beats were noted.

The quinidine dosage was increased gradually until on the fifth day he was receiving 0.5 gm. five times a day. At this point his attacks of syncope ceased. He had then had nine syncopal seizures in five days. Four days after his last attack he was allowed out of bed and the quinidine was discontinued. The lack of medication worried him so placebo pills were substituted. However, he had no more attacks and was discharged on the eighteenth day with instructions to resume quinidine 0.3 gm. at 7 A.M., 2 P.M. and 6 P.M.

A seven-foot roentgen-ray examination of the heart taken during this admission showed a definite increase in the heart size since the previous examination, more marked to the left. Measurements were: Midline to right border 5.2 cm., midline to left border 10.9 cm., great vessels 5.6 cm., internal diameter of the chest 29.0 cm.

Interval History.—The patient returned home and led a sedentary life, taking quinidine three times a day as instructed. On this régime he felt well except for occasional dizzy spells. However, two weeks after discharge he had a typical syncopal attack, and two days later had four more attacks, one of which was said by his family to be particularly severe. He voluntarily increased his quinidine to 0.3 gm. four times a day. The next morning, however, he had another syncopal seizure and finally was advised to reenter the hospital on Dec. 27, 1932, seventeen days after his previous discharge.

Summary of the Third Hospital Admission.—Physical examination was essentially as before. The blood pressure was 170 mm. systolic and 80 mm. diastolic. Regularly occurring extrasystoles caused a coupled heart rhythm.

On the afternoon of admission it was decided to try the effect of immediate withdrawal of the quinidine. At this point the patient had had six attacks in four days. Placebo medication was again substituted, but he had no further attacks, his heart remaining regular at approximately 50.

On the seventh day he was allowed out of bed, and as his activity increased, he again began to have extrasystoles. These gradually increased in frequency until on the fifteenth day periods of coupled rhythm were heard. On the sixteenth day he had another syncopal attack and was again kept in bed. The attacks ceased, but frequent extrasystoles were still heard.

On the seventeenth day quinidine sulphate was resumed. However, he again began to have attacks, and the dosage of quinidine was increased until on the twenty-third day he received 0.6 gm. four times. At this point the attacks again ceased, and as the patient was complaining considerably of vertigo and tinnitus, the dose was cut to 0.4 gm. four times a day where it was maintained. During the preceding seven days he had had eleven attacks.

He then had no further syncopal seizures, and on the twenty-sixth day was allowed out of bed. His heart remained perfectly regular on normal activity about the ward. Quinidine was again discontinued on the thirty-fifth day, no placebos being substituted at this time. That night, eight hours after his last dose of quinidine, he had a spell of transient vertigo, but thereafter his heart rhythm became perfectly regular and remained so through the forty-third day. The patient's general well-being seemed to increase and he felt quite normal.

During this admission he continued to run a slight elevation of temperature to between 99° and 100° F. with a leucocyte count that varied between 14,200 and 7,400 per c. mm. His urine showed a slight trace of albumin on entry, but then cleared completely and phenolsulphonephthalein excretion in the urine was 53 per cent in two hours and ten minutes after intramuscular injection.

DISCUSSION

From the observation of this case, no definite conclusion can be drawn regarding the value of quinidine sulphate in preventing ventricular fibrillation. During the first two admissions it seemed that the increased dosage of quinidine was responsible for the cessation of the syncopal attacks, but withdrawal of the quinidine shortly after entry on the third admission had the same result. A maintenance dose of quinidine kept the patient well for a time, but repeated syncopal attacks were liable to recur and similar periods of freedom from attacks were observed without medication.

The time relations between the attacks and the ingestion of the quinidine were noted on the second and third admissions. Several of the attacks were in the early morning before the first dose. During the second admission the shortest interval was two hours and thirty-five minutes after a dose of 0.3 gm., other short intervals being three and three and one-half hours after doses of 0.5 gm. One attack started five minutes after the drug was taken, but this interval was too short for the quinidine to have taken effect. During the third admission two syncopal attacks occurred one and one-half hours after doses of 0.5 gm. All medication was oral.

It seems logical to conclude that since quinidine prolongs the refractory period of the heart muscle, its use should help to prevent

ventricular fibrillation, as it apparently does ventricular tachycardia. However, Davis and Sprague[3] and Davis[6] believe that it is the normal conduction system that aids in preventing the onset of fibrillation and reason that, if the conduction fibers are already damaged, the toxic effect of the quinidine would further depress their function and outweigh the effect on the ventricular muscle. The drug would, therefore, allow fibrillation to start more easily. Schwartz[7] and Schwartz and Jezer[8] have recently reported several cases of paroxysmal ventricular fibrillation, all of which showed evidences of conduction system damage in the form of complete heart-block. They did not mention the use of quinidine in any of these cases.

The case here reported has shown no evidence of conduction system damage, so should have been an ideal one to demonstrate the value of the drug in preventing fibrillation by its action on the ventricular muscle. Although observation of the case over a period of seven months gives the impression that quinidine sulphate is of some benefit, it has been impossible to prove the fact conclusively.

SUMMARY

A case is reported which showed syncopal attacks proved by the electrocardiograph to be due to transient ventricular fibrillation. The attacks were usually preceded by increasing numbers of ventricular extrasystoles leading into short runs of ventricular tachycardia. Therapy with quinidine sulphate in varying doses was tried over a period of seven months with control periods during which the drug was withheld. During this time there were three hospital admissions. From these observations it seemed that quinidine was of some value, but the effect was not invariable enough to enable one to draw any absolute conclusions as to its efficacy.

I wish to thank Dr. S. A. Levine for his help and suggestions in the preparation of this case report.

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Department of Reviews and Abstracts

Selected Abstracts

Callow, Bessie R.: Bacteriologic Investigation of the Blood in Rheumatic Fever. J. Infect. Dis. **52**: 279, 1933.

The original object of this investigation was to demonstrate the presence or the absence of microorganisms in the blood stream of patients with rheumatic fever. Cultures were made of the blood of 174 patients; 60 per cent of these were subject to blood culture from two to seven times, and a total of 367 cultures was examined. The blood was also studied in a series of patients who gave no history of rheumatic disease.

The frequent isolation of *Streptococcus viridans* and of pleomorphic bacilli from single and repeated blood cultures of patients with rheumatic fever in which the type of organism seemed to bear no relation to the stage or manifestation of the disease and a similar incidence of the same types of organisms in blood cultures of patients with nonrheumatic diseases who gave no history of rheumatic manifestations stimulated a study of the organisms from the point of view of their morphologic and cultural characteristics, biochemical reactions and serologic behavior.

The majority of the strains of *Streptococcus viridans* from blood cultures of rheumatic and nonrheumatic subjects were identified as lanceolate cocci and diplococci, all of which had similar cultural characteristics. A large proportion of the strains tested (63 per cent) fermented mannite and belonged mostly in the *Streptococcus faecalis* group. Other strains from the two sources were grouped with *Streptococcus salivarius* and *Streptococcus mitis*. The application of the bile-heat-esculin test further correlated all diplococcic strains fermenting mannite, whether of rheumatic or nonrheumatic origin, with members of the enterococcus group.

Strains of pleomorphic bacilli from blood cultures of rheumatic and nonrheumatic subjects were similar morphologically, culturally and biochemically.

The bacillary and streptococcic strains varied not only in morphologic and cultural characteristics, effect on red blood cells and serologic reactions, but also in metabolism. The bacillary strains are obligate aerobes, are biologically inactive to sugars and form catalase. The streptococcic strains are facultative anaerobes, are biologically active to sugars, and produce dioxide.

Six experiments are presented which illustrate that under controlled conditions selected strains of pleomorphic bacilli were transformed into diplostreptococci of the green and hemolytic types. The coccic derivatives were similar in all respects to the diplococci originally isolated from the blood cultures of rheumatic and nonrheumatic subjects.

A definite antigenic relationship was established between selected strains of pleomorphic bacilli and their coccic derivatives, also related coccic organisms (both original and derived) by means of reciprocal agglutination and absorption tests. These principles were applied to the study of pleomorphic bacilli and streptococci from repeated blood cultures of the same patient.

Reciprocal agglutination and absorption tests also identified strains of pleomorphic bacilli from repeated blood cultures of several patients and were used in the identification of the coccic derivatives of selected bacillary strains.

It was possible to group 21 streptococcic strains (including 2 strains from patients with subacute bacterial endocarditis and some coccic derivatives) from blood cultures of rheumatic and nonrheumatic subjects into one major group and four subgroups by means of the reciprocal tests. A large series of additional strains from these sources also showed some relationship to the ones in the groups defined. The disease in question, however, whether rheumatic or nonrheumatic, did not appear to be a determining factor in the relationships disclosed.

With one exception, it was not possible to demonstrate agglutinins for the homologous organisms in the serum of patients with rheumatic fever taken at frequent intervals during the course of the disease.

From these studies the author concludes that diplostreptococci (alpha type) and pleomorphic bacilli may be recovered repeatedly from the blood of patients with rheumatic fever and certain diseases mostly of the upper respiratory tract. These organisms apparently represent stages in the life cycle of the same organism. A specific etiologic relationship between these organisms and rheumatic fever is questioned.

Hitchcock, Charles H., and Swift, Homer F.: The Agglutinating Properties of Exudates From Patients With Rheumatic Fever. J. Clin. Investigation 12: 673, 1933.

During the course of a search for agglutinins and precipitins in the body fluids of patients suffering from various acute manifestations of rheumatic fever, it was observed that exudate obtained from the knee during the course of an acute arthritis possessed a marked capacity to cause flocculent growth (thread reaction) of a certain strain of *Streptococcus hemolyticus*. This strain had been kept in the laboratory for many years on artificial media. So striking was this effect noted at times in a dilution of 1:10,000 of the exudate that it seemed desirable to extend the observation to other organisms, as well as to include exudates from conditions other than rheumatic fever.

Joint, pleural and pericardial exudates from patients with rheumatic fever caused clumped growth of certain strains of hemolytic streptococci and staphylococci when tested by the thread reaction. Certain other varieties of bacteria are unaffected. This property is possessed in lesser degree by exudates from nonrheumatic patients.

It was found that old laboratory strains are suitable for demonstration of the reaction, while freshly isolated strains are usually unsuitable. The active material is greatly reduced in potency by heating at 56° C. It is not reactivated by the addition of complement.

It is concluded that these observations have no necessary bearing upon the question of the etiology of rheumatic fever.

Benson, Robert L., Hunter, Warren C., and Manlove, Charles H.: Spontaneous Rupture of the Heart. Report of 40 Cases in Portland, Oregon. Am. J. Path. 9: 295, 1933.

Forty ruptures of the heart have been collected from nearly 7,000 autopsies in Portland, Oregon. One of these was probably of syphilitic origin; another, a dissecting aneurysm of a sinus of Valsalva, was due to *Streptococcus viridans* endocarditis. The remaining 38 ruptures, although in some instances manifesting evidence of syphilis, were attributable to recent or old thrombosis, embolism or

arteriosclerosis of the coronary arteries. The cases are analyzed in detail and classified in groups. They have been studied particularly from the standpoint of location of the rupture. It was noted that in this group cholelithiasis was coincidentally present in 17.5 per cent of the cases.

Herrmann, George, Schwab, E. H., Stone, C. T., and Marr, W. L.: On the Advantage of Alternating the Vegetable and Metallic Diuretics in the Treatment of Edema of Congestive Heart Failure. J. Lab. & Clin. M. **18:** 902, 1933.

Clinical evidence seems to substantiate the idea that purine diuretics act primarily by increasing the glomerular filtration rate, while the heavy metals accomplish their results principally by decreasing the tubular reabsorption. Advantage was taken of these hypothetical considerations of the two different modes of action of the two diuretic drugs in the hope of getting better results by rational combination régimes. Distinctly practical advances in the treatment of the vicious circle of edema in congestive heart failure are demonstrated by the study. The purines and heavy metal diuretics can be so combined (1) as to produce diuresis when either one of the drugs used alone in maximum dose has been ineffectual, (2) as to accomplish the greatest possible diuresis in the shortest interval of time, (3) as to obtain a perfectly satisfactory diuresis by smaller and absolutely harmless doses which alone would prove inadequate.

Zierold, Arthur A.: The Surgical Treatment of Arterial Embolism. J. A. M. A. **101:** 7, 1933.

The author reports a series of 20 cases of auricular embolism in 11 of which surgical treatment was undertaken. The operation consisted of the exposure of the affected vessel at the site of obstruction and the removal of the obstructing embolus and thrombus by arteriotomy. In one case the femoral vein was ligated and the artery was not opened. A discussion of the physical signs by which the cases may be selected for operation together with important secondary procedures in the treatment of these cases is presented.

In view of the fact that arterial emboli are not uncommon phenomena, especially in association with heart disease, this principle of treatment should receive active consideration from physicians. If the location of the embolus can be identified and is in some accessible part, such an operation should be comtemplated. The author believes there is no simple operation in surgery so eminently satisfactory or attended by great potentiality for good as arteriotomy for arterial embolism.

Bass, Murray H., Mond, Herman, Messeloff, Charles R., and Oppenheimer, Enid T.: Systolic Murmurs in Children. J. A. M. A. **101:** 17, 1933.

Sixty-four children with systolic murmurs, both organic and functional were studied clinically and phonocardiographically; the records of all the murmurs contained vibrations of high frequency. Eighty-six per cent of the functional cases presented high-pitched vibrations only, while organic cases revealed low as well as high-pitched vibrations. This suggests an additional means of differentiating between the two types of murmurs.

Irvine-Jones, Edith: Acute Rheumatism as a Familial Disease. A. J. Dis Child. **45:** 1184, 1933.

This study of rheumatism was undertaken to show the relative importance of heredity in constitution contrasted with infectivity as factors in the occurrence of the disease. Five hundred families with rheumatic members were investigated

in St. Louis and Toronto, Canada. These families represented more than 800 rheumatic subjects.

From the study, the impression is confirmed that rheumatism tends to attack more than one member in a family. It has been shown that the incidence in multiple cases in families was about equal in Toronto and St. Louis but that the number infected per family was higher and the age of onset lower in Toronto. Simultaneous attacks were shown to be frequent. It has been shown also that rheumatism is more common in the more distant relatives of rheumatic families than in those of controls. It affected both of two pairs of identical twins simultaneously but only one set of each pair of the dissimilar twins. This condition was also commoner in the families in which the father was affected, which would surely not be the case if contagion were the prime factor. Rheumatism tended to occur in blond and red-haired persons, particularly in those with bluish yellow or hazel eyes, but these characteristics were also found in the nonrheumatic relatives of those persons. The coloring thus had no bearing on the actual occurrence of rheumatism but pointed to a type in which rheumatism frequently occurs.

The author believes from the foregoing evidence that undoubted familial occurrence of rheumatism would seem to be due less to a specific and contagious agent than to certain familial characteristics which favor: (a) the onset of many infections and (b) the appearance of the syndrome known as rheumatism. The determining factor in rheumatism may be nonspecific, since other acute infections of a different nature may arise simultaneously with rheumatic manifestations. Simultaneous attacks of rheumatism would then be explained by some nonspecific but infective agent attacking several people of like "rheumatic" constitution. This is in keeping with the growing opinion of bacteriologists that rheumatism is a specialized type of reaction to a common infective agent.

Wilson, May G., and Edmond, Helen: Blood Cultures in Children With Rheumatic Fever. A. J. Dis. Child. **45**: 1237, 1933.

A total of 236 blood cultures from 67 children with rheumatic disease was studied. In 46 per cent of these children positive cultures were secured. The positive cultures were obtained in 37 per cent during the active stage and in 41 per cent during the apparently inactive period. In a control series which included normal infants and children as well as those who were ill or convalescing from various infections, 153 blood cultures from 78 children and 13 adults were studied. Forty-one per cent of these cultures were positive. The positive cultures were secured in 33 per cent of the healthy infants and children of this control group.

The microorganisms recovered from all the blood cultures were of three types: *Streptococcus viridans, Streptococcus anhemolyticus* and pleomorphic bacilli. About one-half of the organisms recovered were streptococci; the rest were pleomorphic bacilli. The incubation period varied from three to thirty-two days. About one-half of the strains were recovered within a two weeks' period of incubation.

It is concluded from this study that organisms may be recovered from the blood cultures of healthy infants and children and from children acutely ill or convalescing from various infections with this bacteriological method. In view of the results obtained in the control series, the presence of these organisms in the blood cultures of children with rheumatic disease would not appear to be of primary etiological significance. The incidence of recovery of organisms from both the rheumatic and the control series was comparable.

Coombs, Carey F.: Thirty Years' Progress in the Study of Rheumatic Heart Disease. Bristol Med-Chirur. J. **50**: 93, 1933.

This lecture prepared by Dr. Coombs before his death is printed as it was delivered. In it he reviews in interesting and pleasing style the progress that has

been made in our knowledge of this disease. He discusses the early ideas that prevailed among the workers in the English schools at the time the author came under the influence of Dr. Cheadle. He also discusses the present conception of the disease, outlining briefly the various factors that contribute to its incidence.

The main interest in the article centers in the fact that it represents the reflections of one who himself contributed a great deal to the subject and who was constantly in contact with other workers who have played important parts in advancing our knowledge of this condition.

Bohning, Anne, and Katz, Louis N.: Unusual Changes in the Electrocardiograms of Patients With Recent Coronary Occlusion. A. J. M. Sc. **186:** 39, 1933.

Electrocardiograms are presented of ten patients having a clinical history typical of protracted or transient coronary occlusion of recent origin.

The most significant findings in cases of recent coronary occlusion are changes in the form of the S-T segment and the T-wave: either an elevation, a depression or an inversion. The most significant fact is that a definite change is present, whether it be in an upward or in a downward direction. Successive records usually show a rapid change in contour in the early stages of coronary occlusion. Not all curves in recent coronary cases can be fitted into the T_1 and T_3 types of Parkinson and Bedford.

Attention is drawn to a large, upright, sharply peaked T-wave whose limbs and shoulders are symmetrical and have their convexity pointing downward and toward each other, associated with an isoelectric or negative S-T interval having a "hump" pointing down. It is different from the nonspecific, tall T-wave. This large upright T-wave is most commonly found in Leads II and III of the T_1 type and is as diagnostic a feature of the coronary occlusion type of curve as the inverted cove-shaped T-wave of which it is the inverse image. The authors have designated this characteristic as the upright coronary T-wave.

Edeiken, Joseph: The Effect of Spinal Deformities on the Heart. A. J. M. Sc. **186:** 99, 1933.

Spinal deformities, especially scoliosis and kyphoscoliosis have a profound effect upon the lungs, and the effect upon the heart is probably secondary to the latter in most cases. Kinking or twisting of the great vessels as the result of displacement of the heart may be responsible for certain cardiac signs and symptoms.

Most patients with kyphoscoliosis and severe grades of scoliosis have signs of right-sided disturbance of cardiac function. However, they may live for years, many being restricted in activity because of dyspnea on exertion. Some are cyanotic and a few show edema of the legs. According to the literature most patients die of a pulmonary complication.

Kyphoscoliosis causes marked changes in the size, shape and position of the heart. The shape and position of the heart vary considerably from case to case.

The aorta tends to follow the spine in spite of the deformity. In two cases of right kyphoscoliosis observed postmortem, the aorta coursed directly across the thorax to reach the spine.

Pure scoliosis due to organic disease is relatively uncommon and is usually right-sided. In the latter, the heart is displaced and often rotated to the left, causing it to appear "mitralized." The aortic knob appears very sharp in some cases. Left scoliosis causes the heart to become centrally placed and the aortic area to appear widened. The aortic diameter, however, is not increased.

Three of the four cases of kyphosis included in this study presented cardiac complaints but there were complicating factors in each case sufficient to account for the symptoms. In pure kyphosis the anteroposterior transverse diameter ratio tends to be greater than normal.

Two cases of lordosis presented no cardiac symptoms. The anteroposterior transverse diameter ratio was smaller than normal in both.

Except for axis deviation in six instances, the electrocardiogram was normal in 20 of 24 cases of spinal deformity. Two of the four abnormal electrocardiograms were in patients with hyperthyroidism and hypertension. The infrequency of axis deviation despite displacement and rotation of the heart is probably due to the opposing effects of rotation around longitudinal and anteroposterior axes.

Nylin, Gustav: Clinical Tests of the Function of the Heart. Acta Medica Scandinavica, Supplement 52, 1933.

The object of this investigation was to determine before and at fixed times after graduated work, the oxygen consumption, minute volume of the heart, blood pressure and pulse rate, according to a preliminary report.

The increase in oxygen consumption as a percentage of the resting value after a fixed amount of work on the stairs varies within fairly narrow limits in healthy individuals and is independent of body weight, provided that the latter is within physiological limits.

In decompensated heart disease patients and cases of decompensated hypertonia, this increase is consistently greater than in the healthy cases, so that it seems to be a reliable measure of pronounced heart insufficiency, though this is more doubtful with borderline cases. At the same time as the insufficiency yields to treatment, a reduction of the oxygen consumption after work often sets in.

In spite of the paucity of the material, the author believes that the function test according to this method is of practical value in judging as to the presence or otherwise of heart insufficiency, especially in cases of heart neurosis, hypertonia and obesity.

The increase in ventilation after work is a far less reliable measure of the decompensation than the increase in oxygen consumption.

The pulse rate, utilization and standard metabolism, are increased in many decompensated heart disease and hypertonia cases during rest, but, on the other hand, the minute volume, the minute volume/m^2 body surface, and the systolic output, are reduced. Determinations of these functions of the circulation cannot be used, however, as a method of functional heart diagnosis, as the values for healthy and decompensated cases partly overlap.

The systolic output/m^2 body surface in the decompensated cases appears to be considerably reduced, so that its determination is of greater importance than that of the functions mentioned in paragraph 4.

The utilization, i.e., the oxygen absorption per liter of blood, after a fixed amount of work, returns more quickly to the resting value in healthy persons than in severe decompensation cases.

The return of the systolic blood pressure and pulse rate to the resting value, after a fixed amount of work, is slower in decompensation cases than in healthy persons. Owing to the fact that the distribution of the values for healthy persons and decompensation cases partly overlaps, determinations of these functions severally cannot be used as measures of heart insufficiency.

The return of the Liljestrand-Zander's product is retarded in the decompensated cases.

Hinrichsen, Josephine, and Ivy, A. C.: Effect of Stimulation of Visceral Nerves on Coronary Flow in Dogs. Arch. Int. Med. **51**: 932, 1933.

The usual result of stimulating the central end of sensory nerves innervating the upper abdominal viscera or of distending the viscera on coronary flow is an increase in flow. An unquestionable decrease in flow occurred in only two of forty-nine tests, whereas an unquestionable increase in flow occurred in nineteen of thirty-nine tests. In the dog, reflex coronary dilatation is more readily demonstrated than reflex constriction.

The authors are inclined to accept the view of Greene, who has performed similar experiments on the dog, namely, that the failure of the reflex coronary dilator mechanism most likely accounts for the association of angina pectoris with visceral distention or excitation.

Blumgart, Herrman L., Levine, Samuel A., and Berlin, David D.: Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity. Arch. Int. Med. **51**: 866, 1933.

Reasons are given for believing that patients with a normal metabolism who suffer from congestive heart failure or angina pectoris might show striking improvement if the metabolic rate were significantly lowered. The hearts of such people might be unable to supply enough blood for the ordinary demands of a normal metabolic rate but, nevertheless, might be able to supply enough blood for a reduced metabolic rate. The present communication reports the results of producing a subnormal metabolic rate by thyroidectomy on three patients who were suffering from severe congestive heart failure but who showed no evidences of disturbed thyroid function and on one patient with angina pectoris with a slight elevation of metabolism but with a normal gland. In the patients studied the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure.

In two of the three patients with severe congestive heart failure subtotal thyroidectomy caused a fall in the metabolic rate which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowered metabolism and was evidenced by the disappearance of edema, the increased vital capacity of the lungs and the ability to be up and about the ward with comfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level and their clinical conditions became less favorable. One of these patients continued for an additional month to show a somewhat lessened metabolic rate than before operation, and his clinical condition, while not so good as that three weeks following operation, was definitely better than before operation. The patient with angina pectoris has shown no recurrence of the attacks of angina pectoris since subtotal thyroidectomy, although he has returned to work and active life. This is in contrast to his condition before operation, when attacks of angina pectoris occurred even while he was at rest.

In one patient with congestive heart failure complete ablation of all thyroid tissue was done, the parathyroid glands being spared. This patient has maintained his conspicuous clinical improvement, and the metabolic rate has remained persistently lowered for more than six weeks. Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradia-

tion more accurately. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove beneficial is also being studied. In the meantime, the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.

Parsonnet, Aaron E., and Parent, Sol: Auricular Flutter With Complete Auriculo-Ventricular Block in a Patient With Coronary Disease. Arch. Int. Med. **51**: 938, 1933.

A case of auricular flutter with an unusually high auricular rate is reported. This condition was superimposed over a complete dissociation of the auricles and ventricles in a patient who subsequently died with all the classic manifestations of coronary occlusion and infarction. The rarity of such a combination of abnormal rhythms, the extremely high auricular rate, the rapid changes of axis in the various leads, the clear demonstration of flutter configuration in Lead I and finally, the typical T-waves as seen in coronary disturbances are of singular interest.

Hoffman, Arthur M., and Delong, Everett: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage. Arch. Int. Med. **51**: 947, 1933.

A standard technic for obtaining chest leads is presented.

The position of the electrode on the chest is of importance. Uniform tracings can be secured in normal patients by this technic. In diseased hearts, two positions may show abnormal chest leads. Usually, however, only one of these positions shows such an abnormality. When present in both positions, one may revert to normal earlier than the other.

The changes found are not specific for coronary thrombosis, for they were found in other types of myocardial damage confirmed by autopsy. In patients with coronary thrombosis, however, a relatively characteristic chest lead deformity is noticed. Besides Wolferth and Wood's S. T. deformity, the authors found a more frequent abnormality of an isoelectric or upright T-wave in Lead IV. These T-wave abnormalities in the chest lead occasionally precede changes in the standard leads and are, therefore, of value in an earlier confirmation of a diagnosis of coronary thrombosis. They also occur in instances in which the standard leads show the characteristic abnormalities of coronary thrombosis. In some cases of this type, the Lead IV changes may be absent. The chest lead abnormalities change with improvement in the patient's condition, implying that an acute underlying process is taking place. Occasionally a return to normal occurs in the chest lead but not in the standard leads. The reverse of this appears to occur even more frequently.

As pathological changes which occur in the myocardium are not all recorded in either the chest leads or the routine leads alone, the authors feel that it is a worth-while procedure to run the chest leads in all cases of suspected or proved myocardial damage. In all the patients on whom such tracings were taken, in whom there was clinical evidence of heart disease, either the chest lead or the routine leads showed evidence of myocardial damage. In none of these patients were both the routine and the chest leads found to be normal.

Rosenblum, Harold H., and Levine, Samuel A.: What Happens Eventually to Patients With Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? Am. J. M. Sc. **185**: 219, 1933.

A follow-up study was made of 69 "thyrocardiacs" in whom subtotal thyroidectomy was performed. All of these patients before operation had gross evidence of congestive

or anginal heart failure. There were 2 postoperative fatalities, and of the remainder the average length of follow-up was four to five years. Six patients died since the operation after an average survival of 2.5 years. These 6 had been restored either to normal health or to resumption of moderate activities.

Forty-three patients had objective evidence of congestive heart failure; 9 had angina pectoris, 2 of whom had had coronary thrombosis; 15 had definite mitral stenosis and 4 had questionable mitral stenosis; 2 had aortic insufficiency (1 was luetic, 1 rheumatic); 35 patients had hypertensive heart disease.

The average basal metabolic rate before operation was +51.1 and +4.8 per cent after operation. The average preoperative blood pressure was 153 mm. systolic and 81 mm. diastolic. The heart size was practically unchanged as a result of operation. The average preoperative transverse diameter of the heart in 10 patients was 14.3 cm., and postoperatively it was 14.2 cm. All but 7 of the 69 showed some type of heart murmur before operation.

In 27 patients specific notation was made concerning the presence of murmurs before and after operation. All these patients had systolic murmurs and 8 had diastolic murmurs. In 16 instances a preoperative systolic murmur disappeared, in 8 it became less marked, and in 3 it remained unchanged. Of the 8 diastolic murmurs, 6 were due to mitral stenosis and 2 to aortic insufficiency. Three of the former and 1 of the latter first became audible postoperatively.

Of 32 patients who had established auricular fibrillation, 24 were adequately reexamined. Of these 11 had mitral stenosis, and in none of these did the auricular fibrillation spontaneously disappear. Of the remaining 13, 6 reverted to normal rhythm after operation and the cardiac rhythm remained regular for years. There were an additional 11 patients who showed paroxysmal auricular fibrillation. In practically all instances these paroxysms did not recur after the patients left the hospital.

Our experience with quinidin in these cases indicates that it is useless to employ it preoperatively for auricular fibrillation and dangerous to give it postoperatively to those patients with mitral stenosis and auricular fibrillation. It is best given a few weeks after operation to those without mitral stenosis in whom auricular fibrillation is still persisting.

Six cases of paroxysmal auricular flutter occurred in this series. These attacks disappeared permanently in all but 1 of the cases. In the latter instance there was a single return of this arrhythmia associated with some evidence of persisting hyperthyroidism.

Sinus pauses occurred in 2 patients who were both permanently relieved following operation. There were 2 instances of delayed auriculoventricular conduction, 1 of which became normal after subtotal thyroidectomy.

Extrasystoles were relatively uncommon; there were only 6 instances of this irregularity in the group studied.

The great rarity of congestive heart failure in young patients with hyperthyroidism and the almost uniformity of other forms of heart disease (mitral stenosis, hypertension, coronary artery disease, etc.) in those with significant cardiac embarrassment make it probable that hyperthyroidism is rarely the sole cause of heart failure.

The follow-up study of these cases showed that not only was there marked immediate improvement following operation in the various evidences of circulatory embarrassment, such as congestive heart failure, angina pectoris and disturbing irregularities of the heart, but the improvement was extremely well maintained.

The occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure, in whom the thyroid gland was normal, suggests that this operation may be useful more generally in the treatment of various forms of cardiac disease.

Book Reviews

KREISLAUFSTÖRUNGEN UND PATHOLOGISCHE HISTOLOGIE. By Prof. Dr. Martin Nordmann, Privatdozent, University of Tübingen. (Ergebnisse der Kreislaufforschung, Band iv.) 174 pp. Dresden and Leipzig, 1933, Theodor Steinkopff.

This is a review of the literature (for the most part German) dealing with the more manifest disturbances of the circulation in the peripheral vessels, from the clinical as well as the pathological-histological standpoint. It stresses the desirability of many modes of approach to the subject with an attempt at correlation. The author deplores the lack of attention to Rockitansky's point of view. He states that Thoma is the only one who holds with him that phenomena consequent upon circulatory disturbances include all conditions of pathological anatomy. It is an interesting account of the German contributions to the subject of vascular disease.

A. R. B.

DIE BRUSTWANDPULSATIONEN ALS SYMPTOME VON HERZ- UND GEFÄSSKRANKHEITEN. By Dr. Wilhelm Dressler, Assistant in the Heart Station in Vienna. 181 pp., with 87 illustrations. Vienna, 1933, Wilhelm Maudrich.

Dr. Dressler's careful clinical study of pulsations of the chest wall is a notable example of work based on the skillful use of the senses as opposed to a study requiring complicated apparatus. Dr. Dressler reviews the important anatomical and physiological relationships and shows how these affect the pulsations which may be seen or felt in health and in disease. The first part of the book is given over to general considerations; the second to a discussion of the modification of the pulsations under special conditions. The style is clear and the method of presentation interesting. Dr. Dressler has used graphic methods for control purposes, but he has wisely chosen to present his material as a study in physical diagnosis and clinical observation, and as such it should be of special interest to teachers and clinicians.

E. H.

CARDIOVASCULAR PAIN AS A BIOCHEMICAL PROBLEM. By Gordon Lambert, B. A., M.D., B.C. (Cantab.) 75 pages, with 23 illustrations. London, 1933, H. K. Lewis & Co., Ltd.

Contrary to the implication contained in its title, this little monograph proceeds to concern itself with a discussion of the "vascular, muscular and neural factors in cardiovascular pain." There are no original observations. The author has collected seventy-five references, many of them irrelevant. There are frequent quotations, but the recent work of Sir Thomas Lewis is not mentioned. The illustrations consist of crude pen and ink drawings; even the electrocardiograms appear as free-hand sketches.

After sixty-nine pages of futile argument, it is concluded that "biochemical research gives promise of adding to our knowledge, and further compilation of statistics, based solely upon morbid anatomy, cannot yield the same results."

In the opinion of this reviewer, the booklet serves no useful purpose. It neither contributes to our knowledge of cardiovascular pain, nor does it summarize in an adequate manner those facts which are known concerning it.

R. L. L.

Letter to Editor—Correction

Albany, N. Y.,
June 30, 1933.

Through a very regrettable oversight on my part a gross error appeared in my paper "Heart Disease in General Medical Practice," which was published in the April, 1933, issue of the Journal.

On page 7 the statement is made that "from four to eight million people in this country . . . suffer from heart disease." These figures, which are supposed to represent from two to four per cent of the population, clearly should read "from two and one-half to five million."

I shall be grateful to you if you will publish this correction in an early issue of the Journal.

Sincerely yours,

(Signed) J. V. DePorte,

Director, Division of Vital Statistics.

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(An asterisk [*] after a page number indicates that the reference is an abstract and not an original article.)

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